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SYNOPSIS OF TROPICAL MEDICINE

SYNOPSIS OF TROPICAL MEDICINE

SIR PHILIP H. MANSON-BAHR

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PREFACE TO THE THIRD EDITION

Five years have elapsed since the publication of the second edition of this Synopsis. During this time there have been many advances to record in the field of treatment as well as of prophylaxis of the diseases of the tropics.

Tropical Medicine has now become a very large subject and therefore more difficult to keep track of in all its branches, and, although there have been no sensational developments to record on this occasion, comparable to those enunciated in the last edition, advances have been numerous.

The number of drugs and antibiotics in the Tropical Pharmacopoeia has greatly increased, so much so that it has become necessary to create a special section for their tabulation. It takes the place formerly held by a synoptic description of special laboratory methods which have now been outmoded. This drug table has been arranged in alphabetical order with indications and dosages, thus forming an ever-ready and handy reference for treatment. It is hoped that this useful feature may prove of advantage to those who have neither the time nor the opportunity of consulting the larger works on Tropical Medicine.

Philip Manson-Bahr.

149, Harley Street, W.1.

PREFACE TO THE FIRST EDITION

This synopsis has been undertaken in response to numerous requests to provide a guide to tropical medicine in a condensed form, suitable for medical officers in the Armed Forces and others whom the exigencies of the moment call to the tropics.

Though not designed in any way to encroach upon standard textbooks on tropical medicine, this work will, it is hoped, provide adequate information in convenient compass. The material has, as far as possible, been brought up to date and the revision has been undertaken as a small contribution to the war effort.

This task would have been impossible without the aid of those invaluable publications, the *Tropical Diseases Bulletin*, *Bulletin of Hygiene* and *Bulletin of War Medicine*.

My thanks are due to my colleague, Lt.-Col. F. Murgatroyd, R.A.M.C., for undertaking the task of proof correction.

PHILIP MANSON-BAHR.

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SYNOPSIS OF TROPICAL MEDICINE

CHAPTER I

PROTOZOAL DISEASES

MALARIA

Note.—B.T. = Benign tertian; O.T. = Ovale tertian; Q = Quartan; S.T. or M.T. = Subtertian; E.E. = Exo-erythrocytic cycle.

This is the most important tropical fever and is due to four distinct parasites: benign tertian, ovale tertian, quartan and subtertian.

GEOGRAPHICAL DISTRIBUTION

Benign Tertian is widespread in Europe as far as 60° N. and occurred in England until comparatively recently, but is still found in Holland and N. Germany, in N. America, in the valley of Sacramento at 40° N. Its southern range is less extensive: to Natal, Brazil, 30° S. and to S. limits of Argentine at 40° S. It is found rarely (in Himalayas) above 6,000 ft.

Ovale Tertian, closely allied to above, is common in West and Central Africa; isolated cases reported from E. Russia, Egypt, Palestine, Mauritius, Philippines, Venezuela, India and New Guinea.

Quartan is restricted and local; occasionally found in temperate climates in N. Europe; in Mediterranean, S. Italy, Greece, Macedonia, Palestine, Iraq, S. India, Maldive Islands, Andaman Islands, Ceylon, Malaya, sparsely in tropical and subtropical Africa, West Indies (Antigua), Brazil, Panama. In endemic areas it is found especially in children.

Subtertian (or Malignant) has a tropical and subtropical distribution corresponding to the summer isotherm of 70° F. (21° C.) and winter isotherm of 48° F. (9° C.) in Europe, S. Italy, Macedonia, N. Africa, Jordan Valley, Palestine. It is dominant throughout tropical W. and Central Africa, and has a restricted distribution in the plains of Central and S. India, the Duars and Himalayan foothills, S. Malaya, Dutch E. Indies, New Guinea, N. Australia, Queensland, New Hebrides and Solomon Islands; in the New World in the West Indies, Panama, Brazil. In Kenya, in Londiani and Kericho, at 7,800 ft. Wherever malaria is malignant, there subtertian predominates. A virulent form has been transmitted by syringes in heroin addicts in New York, Cairo and Peking. (In this the mortality may be 60 per cent.)

EPIDEMIOLOGY

Malaria incidence usually **endemic;** hyperendemic is a distinct form in which a high degree of transmission induces a high degree of tolerance. Frequency up to 30 times per annum. Infants usually attacked producing annual mortality of 10–20 per mille.

Hypo-endemic.—Spleen rate in children 2–10 years 0–10 per cent.

Meso-endemic.—Spleen rate in children 2–10 years 11–50 per cent.

Hyperendemic.—Spleen rate in children 2–10 years constantly over 75 per cent. Spleen rates in adults high.

Holo-endemic.—Spleen rate in children 2–10 years constantly over 75 per cent. Spleen rates in adults low.

ÆTIOLOGY

The malaria parasite—genus *Plasmodium*—has two main phases: *intracorporeal* in man and *extracorporeal*, or *exogenous*, in mosquito.

The *intracorporeal* has three distinct cycles: asexual (schizogony), sexual (sporogony). While the discovery of an exo-erythrocytic cycle of the malaria parasite in the liver of man has necessitated the creation of a third (see p. 5).

Man is the intermediary: the mosquito is the definitive host in which the sexual cycle is completed.

In all forms of malaria parasite there are *two chromosomes* in the nucleus, one 1 μ in length, the other smaller.

Character of parasites—(Stained with Leishman stain.)

BENIGN TERTIAN (*P. vivax*) asexual cycle.—Ring is distinct, 3 μ across (usually ⅓ diameter of r.b.c.), with conspicuous vacuole and a large nucleus. Attacks mainly reticulocytes. After 30 hours' growth it protrudes amœboid pseudopodia, the corpuscle enlarges, and shows Schüffner's dots. At 36 hours the nucleus splits, the parasites now being 10–12 μ and the host cell twice its normal size; at 48 hours it is a mulberry shaped mass (sporulating body), usually with 16 spores (merozoites), but may have up to 24, and central yellowish brown pigment. Double infection of cell is uncommon.

Sexual cells (gametocytes) in young stage are difficult to differentiate ; when half-grown have no vacuole, and are more solid and more pigmented, but show no clumping of pigment ; male cell is often oval, 7–8 μ across, with chromatin (red) difficult to distinguish from cytoplasm ; it matures in 96 hours. The female gametocyte is 9–10 μ across, oval and round, with blue cytoplasm, small chromatin nucleus, and pigment stippled throughout the cell. Sexual cells appear about nine days after the appearance of parasites in the blood-stream, but do not mature for three days longer ; they probably develop mostly in bone marrow. *P. vivax* is probably capable of surviving in human blood 3–3½ years, after which it dies out. Strains of *P. vivax* are now recognized. *Temperate* in Holland; of low virulence with prolonged latent period of 8 months. Patients infected in autumn develop fever in following summer. *Tropical,* Madagascar and Chesson strains, with incubation period of 12 days, produces fewer merozoites tolerant to N.A.B.

OVALE TERTIAN (*P. ovale*).—Closely resembles *P. vivax* in several respects, but produces only slight enlargement of host cell. Schüffner's dots are profuse. The host cell is usually oval, distorted, with fimbriated margins. The young rings are more solid than *P. vivax* and the chromatin nucleus large. It is a round parasite in an oval cell, rather like quartan in benign tertian cell, but " band forms " are not common and pigment is not so heavy. Half-grown forms are not amœboid. The maximum number of spores (merozoites) is usually 8, but may be 12. Chromatin of the spores is concentric ; and sexual cells (gametocytes) are round and oval, in other respects like those of *P. vivax,* but smaller. *P. ovale* usually causes mild symptoms in man and tends to die out after several paroxysms.

QUARTAN (*P. malariæ*).—Cycle in peripheral blood takes 72 hours. This pigmented parasite has coarse dark-brown pigment. The young rings (trophozoites) have a signet-ring appearance, difficult to distinguish from the ring of benign tertian, with feeble amœboid movement. The host cell is not enlarged. No Schüffner's dots but, with prolonged staining, small fine stippling (James' dots) is seen. Later parasite becomes band-shaped and grows across the corpuscle, forming a solid parasite, with large chromatin mass, and pigment round periphery. At 48 hours it begins to sporulate into 8–12 merozoites (" daisy head "). Parasites are usually scanty in peripheral blood. Sexual cells are like those of *P. vivax,* but smaller. The female (macrogametocyte) stains deeply, and shows a small chromatin mass. The male (microgametocyte) has band-shaped chromatin and stains feebly (dirty colour). The quartan parasite persists in small numbers in the blood for many years (7–19) without causing symptoms.

SUBTERTIAN, malignant (*P. falciparum*).—The cycle is less definite, 48 hours or longer. The rings are small and fine, ⅛ diameter of the corpuscle. In acute stage they are so small as to be easily overlooked, but are larger in the chronic phases. The corpuscle is not enlarged, though often crenated and discoloured ; multiple infections are common and there is a tendency to adhere to the margin of the corpuscle (" accolé," " rim " or " displaced " forms). The chromatin is rod-shaped, often bifid. Rings disappear before the pigment is seen ; pigment is jet black. Larger rings produce " clefts " in corpuscle (Maurer's spots), which stain blue. Clumping of infected cells in the bloodstream resembles the flocculation of blood-grouping. Secondary changes in red corpuscles include polychromasia and basophilic stippling. Development of the sexual and asexual cycle is mostly in the internal

PLATE I

MALARIA PARASITES. (Leishman stained).

Benign Tertian (*Plasmodium vivax*).

1.—Ring form.
2.—Quarter-grown form.
3.—Half-grown form.
4.—Gametocyte.
5.—Sporulating body.

Quartan (*P. malariæ*).

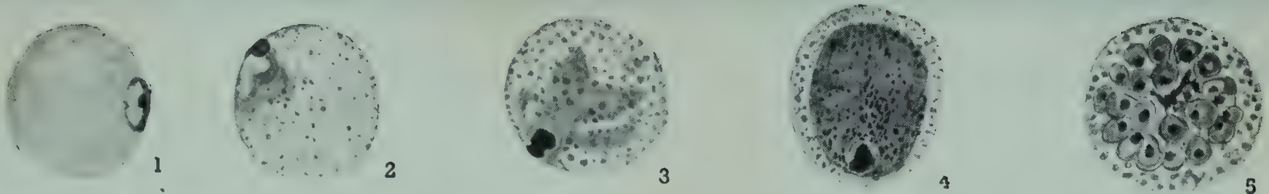
1.—Ring form.
2.—Quarter-grown form.
3.—Half-grown form.
4.—Gametocyte.
5.—Sporulating body.

Ovale Tertian (*P. ovale*).

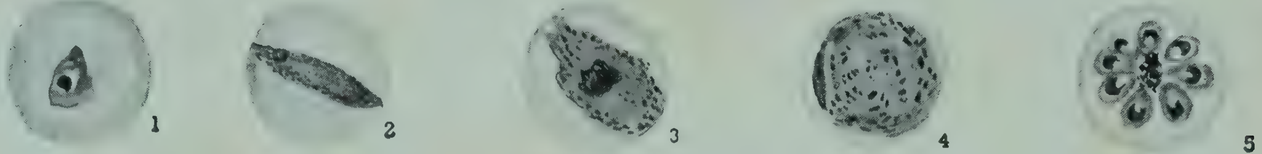
1.—Ring form.
2.—Half-grown form.
3.—Young gametocyte.
4.—Gametocycte.
5.—Sporulating body.

Subtertian (*P. falciparum*).

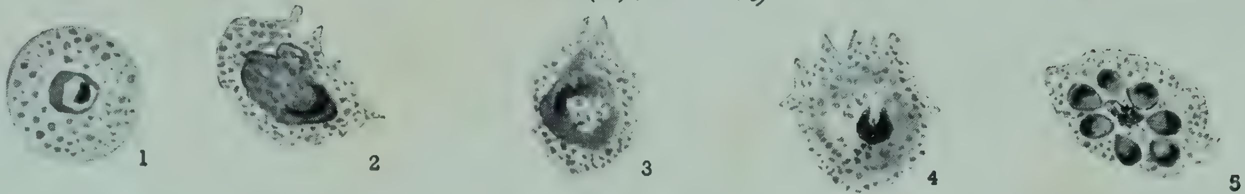
1.—Young ring and accolé forms.
2.—Ring form and Maurer's clefts or spots.
3.—Half-grown form and Maurer's clefts.
4.—Gametocyte (crescent).
5.—Sporulating body.



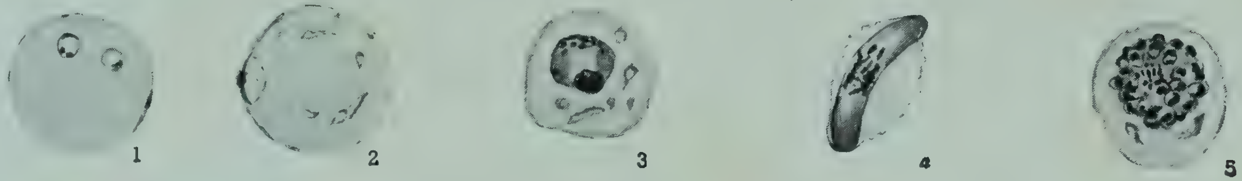
Benign Tertian (B.T) (Plasmodium vivax)



Quartan (Q) (P. malariae)



Ovale Tertian (O.T) (P. cvale)



Subtertian (S.T) (P. falciparum)

Plate I. Malaria Parasites.

capillaries ; the parasites, in spleen, liver and bone-marrow, are small, solid, stain deeply and show no vacuoles. Sporulating forms (0·75–0·8 μ) are rarely seen in blood, mostly in the internal organs, especially in brain capillaries. Merozoites are small (0·75–0·8 μ), about 32 in number. Sporulation (schizogony) does not proceed at the uniform rate of other types. After 48 hours gametocyte (crescents) are produced in cells in the internal organs. At first solid and round without vacuoles, they become crescent-shaped (more like sausages with rounded ends), 9–14 μ by 2–3 μ across (at this stage " Garnham's rod "—inclusion body—dark red, straight or twisted into loop or coil may be seen—like " Cabot's ring "). Crescents appear after an infection has lasted 2–3 weeks, and may persist for six weeks after subsidence of fever. The life span of the crescent is 2–3 weeks. *Male* crescent (gametocyte) is broader and stumpier, with diffuse nucleus and scattered pigment. *Female* stains more deeply, is more slender and has chromatin and pigment concentrated. Young sexual cells can be distinguished from schizonts of same age by their elongated shape and diffuse pigment; the nucleus (chromatin) is small and placed towards one end. There are varieties of *P. falciparum*, some more virulent than others. The large ring form is said to predispose to blackwater fever. *P. tenue*, with more active amœboid movement, may be a subspecies. The subtertian has a much shorter life span in human blood than other species. A single infection persists for one month to one year.

Strains of *P. falciparum* have been separated from W. Africa, Belgian Congo, Italy and Roumania. They vary in virulence in susceptibility to quinine and ability to develop anopheles mosquitoes—*A. maculipennis atroparvus*.

Exogenous cycle in Mosquito. (Anopheles.)—In blood outside body, or in stomach of mosquito, the male sexual cells (*microgametocytes*) exflagellate with six flagella (*microgametes*). The subtertian crescent first becomes round, the pigment undergoing agitation. The female (*macrogametocyte*) also becomes rounded and quiescent. The *microgametes* break away and fertilize the female macrogametocyte which then becomes a *zygote*. After impregnation the cell becomes oval, elongated and capable of independent movement (travelling vermicule or *oökinete*), bores its way into the lining epithelium of the mosquito's stomach and becomes an *oöcyst*. The original nucleus develops rapidly and the protoplasm also segments, forming a spongioplasm, from which *sporozoites* are formed. The cyst bursts and liberates sporozoites, which enter the salivary glands and are injected by mosquito into blood of man with salivary secretion. The sporozoites then enter the liver cells where they undergo a tissue-stage or E.E. cycle.

Under optimum conditions the exogenous cycle in the mosquito takes 8–10 days, but is subject to great variation and is dependent upon temperature and moisture. The optimum conditions are a constant temperature of 68–80° F. (20° C.–27° C.), in association

PLATE II

Diagram of the cycles of *Plasmodium vivax* in man and mosquito (after H. E. Shortt)

(*By permission of the Royal Society of Tropical Medicine & Hygiene*)

1–5. Pre-erythrocytic cycle
  1. Sporozoites from salivary glands of mosquito enter liver cells.
  2. Liver cell containing early stage of pre-erythrocytic parasite.
  3 and 4. Stages in development of the pre-erythrocytic schizont in liver cells.
  5. Fully developed pre-erythrocytic schizont rupturing and releasing pre-erythrocytic merozoites.

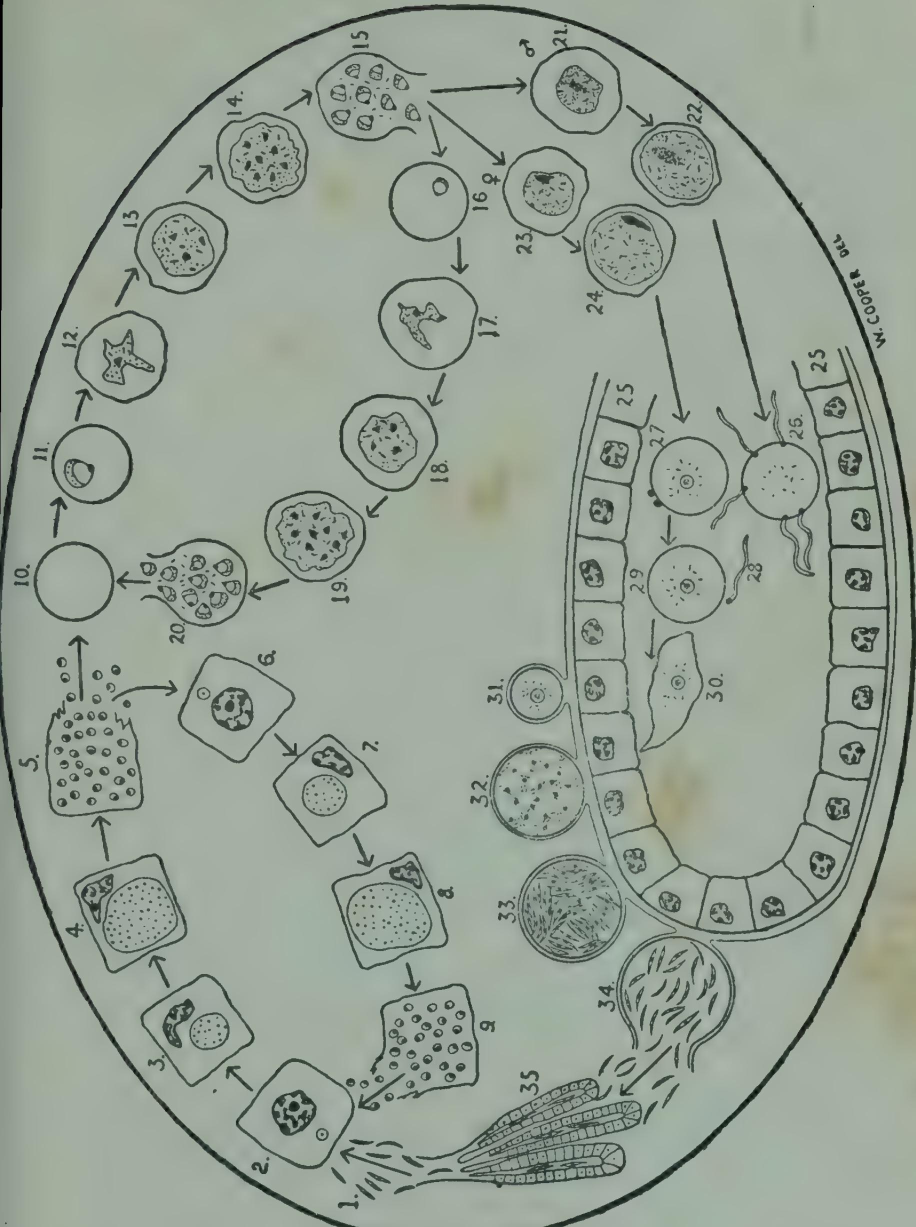
6–9. Exo-erythrocytic cycle.
  6. Liver cell containing merozoite of exo-erythrocytic cycle of schizogony.
  7–9. Remaining stages in exo-erythrocytic schizogony ending in second generation of merozoites.

10–20. Erythrocytic cycle.
  10. Red cell of circulating blood.
  11–14. Stages in erythrocytic schizogony in circulating blood.
  15. Fully developed erythrocytic schizont rupturing and releasing erythrocytic merozoites and gametocytes.
  16–20. Repetition of erythrocytic schizogony.

21–24. Sexual cycle in blood.
  21 and 22. Development of male gametocyte or microgametocyte in circulating blood.
  23 and 24. Development of female gametocyte or macrogametocyte in circulating blood.

25–35. Exogenous or mosquito cycle (definitive host).
  25. Wall of stomach of mosquito.
  26. Exflagellating microgametocyte producing microgametes in stomach of mosquito.
  27. Macrogametocyte extruding polar bodies and so becoming macrogamete.
  28. Microgamete free in stomach of mosquito and seeking macrogamete.
  29. Zygote formed by fertilization of macrogamete by a single microgamete.
  30. Oökinete, or travelling vermicule, formed by elongation of zygote. It is about to penetrate epithelial lining of stomach.
  31. Oöcyst formed by oökinete after penetration of stomach wall of mosquito. It lies under elastic membrane on outer surface of stomach.
  32 and 33. Stages in development of oöcyst with production of sporozoites.
  34. Rupture of mature oöcyst with dispersion of sporozoites most of which enter salivary glands of mosquito.
  35. Salivary gland of mosquito containing mature sporozoites.

PLATE II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with mean relative humidity of 60 per cent. or more. Higher temperatures are usually necessary for *P. falciparum*. As a rule, it takes 10 days for anopheles to become infective with *P. vivax*, 15 days with *P. ovale*. Development ceases at a constant temperature of 60° F. (16° C.). At 68° F. (20° C.) the cycle occupies 16 days for *P. vivax*, 22 for *P. falciparum*, 32 for *P. malariae*.

There are minor differences in the oöcysts in different species. In the case of *P. ovale* the arrangement of the pigment in the oöcyst is distinctive and the sporozoites are more slender and smaller.

Exo-erythrocytic (E.E.) Cycle.—The sporozoites injected into man by the mosquito bite, do not, as postulated originally by Schaudinn, enter the red blood corpuscles and thus initiate the erythrocytic (or blood) cycle of the parasite, but as has been shown so effectively by Shortt, Garnham and others, enter the liver cells where in the course of 7–9 days (representing the incubation period of malaria in man) they develop into a cyst containing large numbers of merozoites (*cryptomerozoites*) which escape into the bloodstream to enter red blood corpuscles and thus to initiate the erythrocytic cycle. The forms within the liver are known as *cryptoschizonts* and this cycle is more properly designated the *pre-erythrocytic cycle*. The mechanism of the malaria relapse is now explained by the entry of some cryptomerozoites into other liver cells where they multiply to form a reservoir so as to produce a relapse on some future occasion. This is properly known as the *exo-erythrocytic* cycle. These stages in the liver are pigmentless. In *P. vivax* infections the fully developed cryptoschizont is 42 μ in length and contains some 800 chromatin masses : that of *P. falciparum* is even larger and contains more numerous *cryptomerozoites*. As far as is at present understood, in *P. falciparum*, the pre-erythrocytic development lasts about 7 days and in *P. vivax* 9 days, whereas in the former development does not proceed further than the pre-erythrocytic phase, in *P. vivax* it passes into the secondary phase and persists in the liver after the parasites have gained access to the bloodstream.

The characters of the tissue phase of *P. ovale* differ from those of *P. vivax* and *P. inui*, but more resemble that of *P. falciparum* in size and form, but whereas the *cryptoschizonts* of the same dimensions in *P. falciparum* produce 40,000 small merozoites, *P. ovale* produces a third of that number and of a larger size. There is evidence of persistence of exo-erythrocytic schizogony in this species as in *P. vivax*.

Congenital Malaria—benign, quartan, subtertian and ovale—have been recorded. Exact manner in which the parasites enter the placenta is not clear. Unless due precautions are observed there is considerable risk in transmitting malaria by *blood transfusion*.

PATHOLOGY

Accounts of pathology and morbid anatomy are based upon subtertian, which is the most virulent and fatal. Pathology of blackwater fever is mainly exaggeration of same process. Pathology correlated to the E.E. cycle of the parasite.

Spleen, birthplace and grave of malaria parasite, is invariably enlarged (ague cake) and highly pigmented with hæmozoin (malaria pigment —hæmatin—formerly melanin). It shows destruction of effete red blood corpuscles by phagocytosis (macrophages—histiocytes), and storage of iron. On section it is purple or chocolate colour, with stretched capsule, diffluent pulp, pale grey Malpighian bodies, immature parasites and pigmented monocytes in branches of splenic artery; small infarctions and necroses.

Liver is congested, enlarged, dark brown ; parenchyma cells contain no hæmozoin, but hæmosiderin and bilirubin ; hæmozoin is deposited in Kupffer cells and parasites in congested sinusoids. Changes are most marked in periphery of lobule. Pigment persists in liver 3–4 months after disappearance of parasites.

Kidneys are congested, with grey dots and lines in pyramids, due to parasites in Bowman's capsules ; convoluted tubules are affected, and there are granular casts.

Placental maternal sinuses are blocked with parasites.

Brain and C.N.S.—*Cerebral cases:* Brain is lead-coloured, with subcortical punctiform hæmorrhages. Capillaries, especially those of corpus striatum and callosum, contain parasites. *Areas of degeneration*—malarial granulomata—focal degeneration, hæmorrhages and glial proliferation—are seen.

CLINICAL PATHOLOGY

Blood shows rapid destruction of red blood corpuscles (count may fall below one million), poikilocytosis, anisocytosis, polychromasia, basophilic stippling, reticulocytosis, monoblasts, Cabot's rings and other signs of degeneration, megalocytes, occasional normoblasts, clumping of red cells, and increased sedimentation rate. One parasite to 100,000 r.b.c. necessary to produce symptoms. There is hæmolysis of parasitized and also unparasitized cells. Hæmozoin may act as hæmolysin. Damage to reticulo-endothelium is important. *Leucocytes* are increased in paroxysm ; subsequent leucopenia. Relative increase of large mononuclears even after quinine treatment (15 per cent. is diagnostic); may be pigmented; diminution of blood platelets. *Fluid elements:* decrease in total protein, decrease in albumin; increase of euglobulin and serum bilirubin. Indirect Van den Bergh reaction.

Malaria pigment, hæmozoin (hæmatin), is insoluble, even in strong acids, formed within parasites, and contains firmly combined iron. Hæmosiderin (derived from hæmoglobin destruction in parenchyma cells of liver, spleen, pancreas, bone marrow, connective tissue cells) contains free iron and gives Prussian-blue reaction.

Hæmofuscin, iron-free, yellow, is present in organs in chronic malaria. Polycholia results from excessive blood destruction.

Urine.—Increased in amount; chlorides and urea increased in ague; phosphates decreased in rigor, increased in sweating stage. Transient albuminuria and glycosuria common. Urobilinogen and urobilin increased as result of hæmolysis.

General Statement.—The number of parasites necessary to produce fever depends not so much on their prevalence, as on the degree of tolerance of the host. They differ in the first, second and third relapses, and so on. Thus, in the primary attack prolonged search may reveal no parasites on the first day and as long as the third. On the other hand in relapse 3,000 or more may be found, of which a considerable proportion may be gametocytes.

CLINICAL FEATURES

Incubation period: 10 days; laboratory infection: 14 days; may lie latent for six months, especially benign tertian more rarely subtertian. Clinical appearances are greatly modified by the degree of immunity. In hyperendemic areas it may produce no symptoms, especially in *P. falciparum* infections, when parasites are present in numbers in the peripheral blood without fever.

Premonitory: Lassitude, headache, bone pains.

Ague fit: Rigor—cold stage, 1–2 hours, vomiting, skin cold and blue, temperature rises, convulsions in children.

Hot stage: 3–4 hours, feeling of warmth, headache intense, pulse full and bounding, rapid respiration, T. 104–106° F.

Sweating stage: 2–4 hours, sweating ++, feeling of relief, T. subnormal. Herpes of lips and nose common.

Spleen enlarges during rigor, and is usually, but not necessarily, palpable, especially in subtertian. Liver enlarged and painful. Typical ague in benign tertian, quartan and ovale tertian; seldom in subtertian.

B.T., characterized by tendency to relapse, after long quiescent intervals six months to one year. Tertian periodicity with fever every 48 hours. Initial fever may be irregular and uncharacteristic. *O.T.*, practically symptomless, but may simulate subacute appendicitis or rheumatism. In self-induced *ovale* infections Garnham noticed severe attacks with irregular fever, of rough tertian periodicity and persisting 3 weeks. Persistent headache was a feature of short-term relapses. *Q.*, particularly persistent and symptomless, with liability to *nephrosis*.

S.T., great variations, *e.g.*, may be afebrile and symptomless or parasite may be latent for months. Liability to explosions. Rigor stage relatively less marked; produces severe anæmia. Involvement of internal organs may simulate many other diseases.

Forms of S.T.—Bilious remittent: Severe fever, bilious vomiting, enlarged painful spleen and liver; may resemble yellow fever or simulate typhoid ("typhoid remittent").

Pernicious attacks; hyperpyrexia, delirium +, coma, mania, epileptiform convulsions, cerebral paralysis; may resemble uræmic or diabetic coma, pontine hæmorrhage or cerebrospinal meningitis. Psychical disturbances and loss of memory may ensue. Many phenomena are physiological and due to anoxia.

Algid forms: Gastric: with vomiting, epigastric pain, sometimes hæmatemesis, resembling gastric disease.

Choleraic: Profuse diarrhœa, with collapse (peripheral vascular failure), simulating cholera.

Dysenteric: Blood and mucus in stools, resembling bacillary dysentery.

Purpuric: Intradermal hæmorrhages.

Oedematous: General anarsarca, resembling cardiac beriberi.

Syncopal: Acute heart failure, resembling cardiac disease.

Acute anæmic: Hæmolytic anæmia, resembling pernicious anæmia.

Nephritic: Blood and casts in urine, resembling acute nephritis.

Gangrenous: Gangrene of extremities may occur.

Appendicular: Pain in right iliac fossa, resembling appendicitis.

Cholecystitic: Pain over gall-bladder, resembling acute cholecystitis.

Icteric: Deep jaundice, resembling yellow fever, Weil's disease or infective jaundice.

S.T. malaria is particularly severe in children.

SEQUELÆ

The main sequel is *Blackwater Fever;* acute hæmolysis of red blood corpuscles liberating hæmoglobin which produces hæmoglobinuria, pigment in urinary tubules and anuria. Has same geographical distribution as subtertian malaria and occurs mostly in sensitized individuals, *i.e.*, those long resident in endemic zone and subjected to frequent infections with S.T. parasite. Rare, if ever, after primary attack ; rare in natives of endemic zone, unless protected from malarial infection in infancy, as now in W. Africa. Cold, exertion, alcohol and excessive quinine predispose to attack. It is now generally acknowledged that quinine is the chief excitant in the production of hæmolysis. This is shown by the practical disappearance of blackwater since the introduction of modern antimalarials. Malaria parasites are usually destroyed by hæmolysis, but may persist; malaria infection can be transmitted to non-immune by blackwater blood. Mechanism of hæmolysis not known, possibly allergic.

Hæmatin, set free, combines with serum albumin to form methæmalbumin ; stored in liver, not excreted in urine. Oxyhæmoglobin is converted into methæmoglobin, which is excreted. Mechanism of anuria is not due to blockage of urinary tubules. as formerly supposed, but to renal anoxia (Maegraith and Havard), on analogy with surgical shock, cholera and renal failure. In oliguria and anuria (tubulo-vascular syndrome), kidney changes are produced by lack of oxygen, resulting from alterations in the renal blood flow. Great anæmia; half r.b.c.s. destroyed. Death from anoxæmia, cardiac failure, pernicious vomiting, anuria. Pathology resembles exaggerated subtertian malaria with maximum onus on kidneys. Histological changes resemble those of incompatible blood transfusion.

CLINICAL.—Enlarged painful spleen, sudden onset, rigor, polyuria, black (porter coloured) urine—methæmoglobinuria. Bilious vomiting +, hæmolytic icterus on 3rd day, after which urine clears and contains bilirubin, urobilin + and casts. Suppression of urine on 8th day, or later. Death may occur later from convulsions, coma or complications, pneumonia, streptococcal septicæmia, etc. Pigmented gallstones may be a sequel. Relapses may occur ; one attack predisposes to second or third (usually fatal), but individuals may survive many attacks. Retinal hæmorrhages may occur. Death-rate in Africa may be 50 per cent. ; usually 25 per cent. Blackwater fever not infrequent in temperate climates in malaria-infected patients from tropics. Has been seen in children ; is especially dangerous in pregnant women. Those with predisposition to blackwater should not return to the tropics.

Other sequelæ of malaria.—Malarial cachexia : splenomegaly (ague cake) ; retarded development in children. Abortion in pregnant women. Rupture of spleen. *Splenic index* is guide to endemicity of malaria in district (50 per cent. hyperendemic, 25 per cent. highly endemic, 10 per cent. moderately endemic). Spleen rate specially valuable in children. *Parasite index* reliable up to five years of age, less reliable afterwards.

Immunity to malaria gradually acquired in childhood ; most adult natives relatively immune. " White man big fever ; black man little fever." Balance between resistance to organisms and tendency of parasites to multiply = premunition. Parasites frequently found in Africans otherwise in good health.

DIAGNOSIS

Blood examination by thin and thick film methods ; latter is more reliable in mass surveys. In quiescent period diagnosis by increase of mononuclears and pigmented leucocytes. Diagnosis by therapeutic action of quinine or atebrin (mepacrine hydrochloride) or other antimalarials not recommended, and only permissible when microscopic diagnosis is unobtainable.

DIAGNOSIS BY CLINICAL SIGNS.—Character of fever, periodicity, splenomegaly, persisting urobilinuria, patient's history (often unreliable) ; malaria rigors are simulated by genito-urinary and other infections. Splenic and sternal puncture have been employed ; intravenous adrenaline may provoke attack. Blackwater to be distinguished from paroxysmal hæmoglobinuria, Weil's disease (leptospirosis), favism and acute quinine poisoning.

TREATMENT

The state of immunity naturally affects the use of antimalarial drugs and in these cases the dosages given below may require modification.

Quinine efficacious in B.T. and in S.T., but may precipitate blackwater fever in latter. Less effective in Q. Quinine is to some extent superseded by introduction of synthetic drugs.

Quinine sulphate is insoluble and acid sulph. dil. must be added to it ; hydrochloride fairly soluble ; dihydrochloride easily soluble and suitable for parenteral injection. Lacquin (milk) preparation containing quinine ethyl carbonate, with disguised taste, is suitable for children.

Dosage.—Heroic doses inefficacious, dangerous and do not extirpate infection. Maximum dosage 30 gr. (1·94 gm.). Most infections react to 20 gr. (1·29 gm.). Children have 1/20th adult dose. Rational dosage : gr. 30 for 3 days, gr. 20 for 7 days. Anti-relapse treatment : gr. 10 (0·64 gm.) for 4 weeks.

Toxic effects.—*Quinine idiosyncrasy:* dyspepsia, urticaria, skin sensitivity to scratch test. *Quinine amblyopia:* spasm of retinal artery; blindness in overdosage. In pregnancy, very rarely, may produce *miscarriage.* In excessive doses, quinine *hæmoglobinuria,* resembling blackwater.

Excretion of quinine in urine is controlled by Mayer-Tanret reaction (mercuric chloride 27 gm. in 1500 c.c. water, pot. iod. 100 gm. in 500 water, mixed, add 25 c.c. glacial acetic acid—turbidity produced) and by coating quinine tablets with methylene blue, so that it is readily recognizable in urine of large groups.

Injection of quinine: Intramuscular into buttocks above gluteal fold, gr. 10 (0·64 gm.) maximum. Dissolve in 5 c.c. water, inject slowly, massage part. Not more than three injections on successive days. Dangers : abscess, septicæmia, tetanus, painful fibrotic nodules and, when into sciatic nerve, paralysis of leg.

Intravenous quinine dihydrochloride for cerebral and algid forms of subtertian malaria. Not more than 10 gr. (0·64 gm.) in 10 c.c. water (or 5 per cent. glucose) combined with 10 min. (0·6 c.c.) of 1 : 1000 adrenaline. Inject *slowly.*

Synthetic antimalarial drugs.—*Atebrin* (mepacrine hydrochloride, quinacrine)—yellow dye—specially indicated for S.T., gives effect comparable to quinine on rings (trophozoites), but not on gametocytes (crescents); effect on fever not so rapid as quinine. Dose: 1½ gr. (0·1 gm.) t.d.s. for 7 days on full stomach. For full cure, repeat course after interval of 5 days. In virulent S.T. cases, combine with quinine: atebrin 4½ gr. (0·3 gm.), quinine, 10 gr. (0·64 gm.) daily. In acute attack larger doses now advocated up to 0·9 gm. for 2–3 days—not longer. Atebrin staining of skin is necessary to obtain full effects.

Atebrin by injection (atebrin musonate), intramuscularly or intravenously, should be reserved for pernicious attacks of S.T. *Toxic effects:* epigastric pain, vomiting and yellow pigmentation of skin, especially face; and in susceptible individuals (Malays) cerebral excitement. Skin eruptions and lichen planus of legs may ensue after prolonged atebrin therapy. Maroon-coloured discolouration of base of nails is also a sign of chronic atebrin poisoning.

Paludrine (*Proguanil.* M 4888) is N.-*p*-chlorophenyl-N5-isopropylbiguanide acetate. Acts on the E.E. forms. This renders it an ideal prophylactic for human malaria as it appears to be singularly devoid of toxic properties and is equally effective against all forms of human malaria. On large scale immediate results appeared to be satisfactory, but recently it has been found that malaria parasites, especially the benign tertian, readily become paludrine-resistant which seriously interferes with the general application of this drug.

Paludrine is not so rapid in its action as is quinine, atebrin or chloroquine and therefore should not be employed for the treatment of serious cases of subtertian malaria, especially the cerebral forms. For a clinical case of subtertian malaria of average severity the dose is 300 mgm. daily for 10 days. A suppressive dose is 100 mgm. daily.

Chloroquine (*Aralen, Resorchin, Nivaquine, Avlochlor*) is active in all forms of malaria. Tablets of 0·25 grm. (150 mgm. of base). Loading dose is 4 tablets, second dose 6 hours later of 2 tablets, then 2 tablets on each of next 2 days.

Amodiaquine (*Camoquine*).—Tablets of 0·2 grm. (200 mgm. of base). Loading dose 3 tablets; on each of the following days 2 tablets.

Daraprim (*Pyrimethamine*).—Tablets of 0·025 grm. (25 mgm. of base). One or two tablets daily, especially for B.T.

Primaquine (*Pentaquine*) is a 4-aminoquinoline and like its predecessor, pamaquine, is apt to be toxic and produce hæmolysis, especially in negroes and Indians. It has been most effective as a suppressant in B.T. malaria. The doses are small, in tablets 6·5 mgm. Prolonged treatment of 60 mgm. with 20 grs. of quinine daily eradicates *P. vivax*.

Treatment of cerebral malaria.—Intravenous quinine dihydrochloride gr. 10 (0·64 gm.), inhalation of oxygen, amyl nitrite. Intravenous nor-adrenaline 10 min. (0·6 c.c.) to counteract peripheral vascular failure. Lumbar puncture (fluid is under increased pressure and may contain cells and hæmozoin). Subsequently, intravenous plasma and glucose 10 per cent. 20 oz. (591 c.c.), every 5–6 hours.

Treatment of hyperpyrexia (106° F., 41·5° C.).—Hydrotherapy.

Treatment of malaria patients on return from tropics.—Paludrine is administered in doses of 100 mgm. daily for seven days prior to arrival in a malarious country and for one month after return to Europe.

Treatment of Blackwater Fever.—Treatment in bed as for shock. Copious fluids by mouth, if vomiting not too severe ; morphia for restlessness or if necessary to transport patient to hospital. Intravenous sodium bicarbonate 150 gr. (10 gm.) to 1 pint (591 c.c.), after which glucose-D by mouth and intravenously, 5 per cent., 7 ozs. (206 c.c.). For diuresis : caffeine citrate, gr. 5, t.d.s. For suppression of urine : high colonic lavage with hot salines or continuous intrarectal drip saline. For vomiting : turpentine stupes, or mustard plaster to epigastrium. *Tab. atebrin* (mepacrine hydrochloride) 4½ gr. (0·3 gm.) daily for 5–7 days prevents malaria

Other antimalarials.—As so many active drugs have been introduced the results can be summarized in a table.

	Effect on Clinical attacks		*Value as preventive*		*Toxicity*
	S.T.	*B.T.*	*S.T.*	*B.T.*	
1 Quinine	Often radical cure	Clinical cure	Poor suppressant	Poor suppressant	Moderate
2 Mepacrine (Atebrin) ..	Radical cure	Clinical cure	Complete suppressant	Good suppressant	Moderate
3 Chloroquine	Radical cure	Clinical cure	Complete suppressant	Good suppressant	Low
4 Amodiaquine (Camoquine)	Radical cure	Clinical cure	Complete suppressant	Good suppressant	Low
5 Proguanil (Paludrine)	Often radical cure	Clinical cure	True prophylactic	Good suppressant	Very slight
6 Pyrimethamine (Daraprim)	Often radical cure	Clinical cure	True prophylactic	Very good suppressant	Slight
7 Pamaquine (Plasmoquine).	Cures, but only when given in dangerous doses.		Prevents, but only when given in dangerous doses.		High
8 Primaquine or Pentaquine..	Radical cure in non-toxic doses given for a limited period.		True prophylactic when given in non-toxic doses for a limited period, e.g. 14 days.		Moderate
9 Proguanil (Paludrine) *plus* mepacrine or *plus* quinine ..	Radical cure	Clinical cure	Not used	Not used	Very low
10 Quinine or mepacrine *plus* either pamaquine or primaquine.. ..	Radical cure	Radical cure	Not used	Not used	As for 7 & 8
11 Chloroquine or amodiaquine *plus* primaquine	Radical cure	Radical cure	Not used	Not used	Least toxic combination

relapse. Blood transfusion (carefully grouped), of 300–500 c.c. combats hæmolysis and shock, is a life-saving measure and may be repeated.

AFTER TREATMENT.—Liver injections and massive iron by mouth. If spleen still enlarged, further treatment with atebrin or paludrine to prevent possible relapse. Return to tropics inadvisable, especially after two attacks.

PROPHYLAXIS

Definition.

(*a*) **Gametocyte prophylaxis.**

Prevention of infection through action of drugs—primaquine (pentaquine)—on gametocytes or their precursors in human body.

(*b*) **Causal prophylaxis.**

Prevention of infection by human host through action of drugs on the sporozoites or upon intermediate stages of the malaria parasites in the body.

(*c*) **Suppressive prophylaxis.**

Prevention of development of clinical manifestations of sub-patent infections by means of action of drugs on the asexual forms.

Anti-mosquito measures.

ANOPHELES MOSQUITOES world wide, but specially abundant in tropics; genus includes 180 known species, many with limited geographical distribution. Differ from other mosquitoes in the following respects. In female, palps are as long as proboscis and closely applied. Wings usually spotted, sometimes gaily marked with scales; scutellum (posterior margin of thorax) rounded. Resting position oblique or perpendicular, with proboscis, head and abdomen in straight line—resembles splinter at angle from surface of wall; commonly seen in daytime, resting on ceiling and angles of wall. Hum produced by wings is low-pitched, almost inaudible. Eggs are boat-shaped, will float, laid singly on water; larvæ lie horizontally on surface. Respiratory siphon absent, but opening composed of two laterally-placed spiracles on eighth abdominal segment; position maintained by row of palmate hairs on dorsal surface. (Contrast with long respiratory siphon and vertical position maintained by larvæ of other genera of mosquito, also horizontal resting position adopted by adults.)

IMPORTANT SPECIES.

A. maculipennis, Europe, N. Africa, N. America. Some races *anthropophilic* (live on man) in S. Europe; others *zoophilic*: prefer blood of animals, *e.g.*, cattle in N. Europe.

Subspecies "*atroparvus*" breeds in salt water; *messeæ* in fresh water and *labranchiæ* feeds on man, convey malaria; *typicus*, *melanoon* and *messeæ* feed on cattle, latter hibernates; not important carriers.

A. gambiæ, widespread and dangerous carrier in Africa. Introduced in 1930 into Brazil, had spread widely inland. Breeds in any collection of water. Also **A. funestus.** In N. Africa, **A. multicolor.**

A. stephensi, India, chief malaria-carrier in Bombay ; breeds mostly in wells and cisterns.

A. subpictus, in Java breeds in brackish, polluted pools.

A. maculatus, Indonesia and Malaya, breeds in streams in foothills.

A. minimus, fluviatilis, varuna and **aconitus,** breed in streams and irrigated rice fields in India, Ceylon and Indo-China.

A. culicifacies, with highly spotted wings, and horizontal " **stance** " of culex mosquito. Chief carrier in Ceylon, breeds mainly in pools or dried-up river beds.

In N. America, three species : **A. maculipennis** (*occidentalis*). **A. punctipennis, A. pseudopunctipennis**—breed in sunlit pools.

In S. America: **A. albimanus,** Mexico and Caribbean, **quadrimaculatus** E.C. and S.U.S.A. ; **A. darlingi, A. aquasalis,** Guianas, Brazil and Venezuela. Breeds in salt water. **A.** (*Kerteszia*) **bellator,** Trinidad, breeds in epiphytic bromeliads.

In New Guinea and Polynesia: **A. punctulatus, A. farauti** (*moluccensis*) and **A. annulipes** breed in stagnant pools with abundance of algæ.

Species sanitation.—Measures adapted to habits of each particular carrier in endemic areas ; cost important ; methods vary according to circumstances, *e.g.*, length of residence in area, military operations, engineering works, permanent plantations.

CHIEF METHODS.

1. **Make place unsuitable for adult anopheles and larvæ.**—Drain swamps—but these are often not dangerous ; fill in holes and borrow pits ; prevent making of holes and pits ; improve drainage; camber surface of roads ; train streams ; give periodic flushings. Make communications of salt marshes open to sea effective, so that their water is too salt for larvæ. Shade streams (*i.e.*, with Lantana) ; cut out light and air and diminish vegetation : this is effective against *A. minimus* in India and Malaya and *A. funestus* in Africa.
2. **Avoid adult mosquitoes.**—Keep houses airy and light, with no dark corners. In tropics anopheles enter at night ; draughts and breezes drive them out during day.
3. **Destroy adults.**—Very effective, especially against races of *A. maculipennis* and in India against *A. culicifacies.* Usually in tropics dangerous species of anophelines can be swatted in bedroom. Clear room of mosquitoes before retiring ; do not show light at open windows. Spray rooms with DDT and pyrethrum once or twice a week, especially in autumn and during cold weather. This ensures a quick " knock-down." DDT (dichlor-diphenyl-trichlorethane) is lethal to wide range of insects and the dose varies greatly. On the whole it is more toxic to anophelines than to culicines. In solutions of 3–5 per cent. in kerosene it produces a residual film on walls and ceilings and kills adult mosquitoes in houses. Fine atomizing guns create mists which tend to float away. DDT can be incorporated in paint or distemper when it retains some of its insecticidal properties and thus assists in

destroying anophelines in houses. Especially effective with anthrophilic mosquitoes such as *A. darlingi* and *A. aquasalis* in British Guiana. The residual spraying of adults leads to reduction of larvæ as well. The prolonged residual action of DDT is of greatest value for adult mosquito destruction. Malaria now banished from Sardinia, Cyprus and from British Guiana.

DDT-resistant strains of anopheles especially *A. culicifacies*, are being produced. There are a number of efficienc insecticides, at least 22, now available. Of these, chlordane, dieldrin, aldrin, benzene hexachloride (BHC) or gammexane, are available.

4. **Destroy larvæ.**—To prepare a 5 per cent. DDT solution ½ lb. of finely powdered DDT is ground finely and mixed with 1 gallon of kerosene or Diesel oil. In India the best results have been obtained by residual spraying indoors after aircraft spraying outdoors.

5. **Poison mosquito foods.**—DDT emulsions mixed with finely powdered cork spread over surface of water or dusted from aeroplanes now considered most effective. Generally speaking 2–4 oz. DDT per acre suffices to control anopheline larvæ. Paris green (copper aceto-arsenite) not used pure, powdered to standard fineness, is mixed 1–4 parts to 100 parts dry powdered lime, ashes, flour or powdered soapstone. Discharged by powder blower, spread by aeroplane. Dry dust floats for some hours ; larvæ eat particles and are poisoned. Not dangerous to fish or man if used this way. Effective against anopheles because they are surface feeders.

6. **Introduce enemies.**—Small fishes eat larvæ : local species usually well known, *e.g.*, *Gambusia* (" millions " or " top minnows "), surface feeders which stand heat and cold. Cut weeds to give access to larvæ. Maintain nurseries. *Gambusia* is viviparous and cannibal, useful in wells, especially in Bombay against *A. stephensi*, or in ponds against *A. maculipennis*.

7. **Protect from bites of Anopheles.**—Screening of houses, double doors, etc., effective if properly done ; otherwise dangerous. *Mosquito nets*, 25–26 holes to sq. in. (trade term really meaning 150 holes to sq. in.). Net should not be too large, nor so narrow as to permit arms and legs to be bitten through netting. Edges of net tucked in below mattress or weighted with lead weights if it reaches to floor. Net suspended from framework. Roll up during daytime. Can be impregnated with D.M.P.

Repellents are not really satisfactory ; anti-mosquito cream contains oil of citronella. cedarwood oil and camphor with white petroleum jelly. Dimethyl phthalate (D.M.P.) (see p. 247) is recommended in Malaya as an effective repellent. Sketofax cream and Dimeepol both contain D.M.P. Mosquito boots protect legs. Joss sticks burned under tables deter mosquitoes. Veils and gloves protect sentries on night duty. Fumigation with pyrethrum powder or " Flit " kills mosquitoes in rooms.

8. **Site selection.**—Houses, tents and lines should be remote from breeding places. Distance mosquitoes can fly depends on number of mosquitoes, direction and force of wind, and intervening cover ;

some species are more powerful than others: ½ mile distance usually effective, but exceptions occur.

9. **Animal prophylaxis.**—Deflection by animals—mainly cattle—works with *A. hyrcanus* especially, but if animals are few, this method is dangerous. *A. gambiæ* and *A. minimus* cannot be thus deflected.
10. **Drug prophylaxis.**—*Chemoprophylaxis:* taking quinine was formerly a daily regular practice in tropics, mainly in W. Africa. *Atebrin* (mepacrine hydrochloride) prophylaxis has been much used. Drug is retained in body, is not toxic, does not upset digestion. Children tolerate atebrin up to 0·2 gm. for 4–6 days in the week. The dose advocated is 0·1 gm (1½ gr.) daily for 6 days in the week, or 0·6 gm. weekly.

Chloroquine, 2 tablets once weekly, is well tolerated and is popular, but it is essentially a suppressant and not a true prophylactic as it does not kill the pre-erythrocytic forms in the liver. According to modern ideas the drugs for susceptible, or none immune, persons advocated are as follows:—

(1) Daraprim (pyrimethamine), 1 tablet (each 25 mgm.) once weekly.
(2) Paludrine (proguanil), 1 tablet (each 100 mgm.) once daily.
(3) Chloroquine, 2 tablets (each 150 mgm. base) once weekly.
(4) Amodiaquine (camoquine), 2 tablets (each 200 mgm. base) once weekly.

The selected drug is commenced on arrival in the malarious district and continued for a week after leaving it for (1) and (2), and one month for (3) and (4). In Central, E. and W. Africa twice the above dosage of paludrine and a bi-weekly dose of daraprim is advised.

The equivalent number of tablets for children according to age is:—

	16+	11–15	7–10	4–6	1–3	under 1
Daraprim ..	1	1	¾	½	¼	¼
Paludrine ..	1	1	¾	½	¼	¼
Chloroquine ..	2	1½	1	¾	½	¼
Amodiaquine ..	2	1½	1	¾	½	¼

Value of prophylactic measures:—

Mosquito protection, drug prophylaxis ..	1·7%	infected
Mosquito protection alone	2·5%	,,
No protection	33·0%	,,

LEISHMANIASIS

Note.—K.A. = Kala-azar, L.D. = Leishman-Donovan body, O.S. = Oriental sore, Es. = Espundia.

A group of diseases of most varied appearances associated with organism *Leishmania*, morphologically identical:—

A. Visceral leishmaniasis, invasion of reticulo-endothelium—**Kala-azar** (a malaria-like disease).
B. Cutaneous leishmaniasis—**Oriental sore.**
C. Muco-cutaneous nasopharyngeal leishmaniasis—**Espundia,** causing great destruction and disfigurement.

PLATE III

LEISHMAN-DONOVAN BODIES IN KALA-AZAR AND RELATED FORMS

1.—Leishman-Donovan bodies in endothelial cells in film from spleen puncture.
2.—Free forms of Leishman-Donovan bodies from spleen.
3.—Developmental forms of *Leishmania donovani* from the leishman body to the crithidial stage, and clumping of the flagellated organisms.
4.—Parasites enclosed within splenic pulp cells, as seen in section stained with hæmatoxylin.
5.—Diagram of Leishman-Donovan body, greatly enlarged, highly magnified.

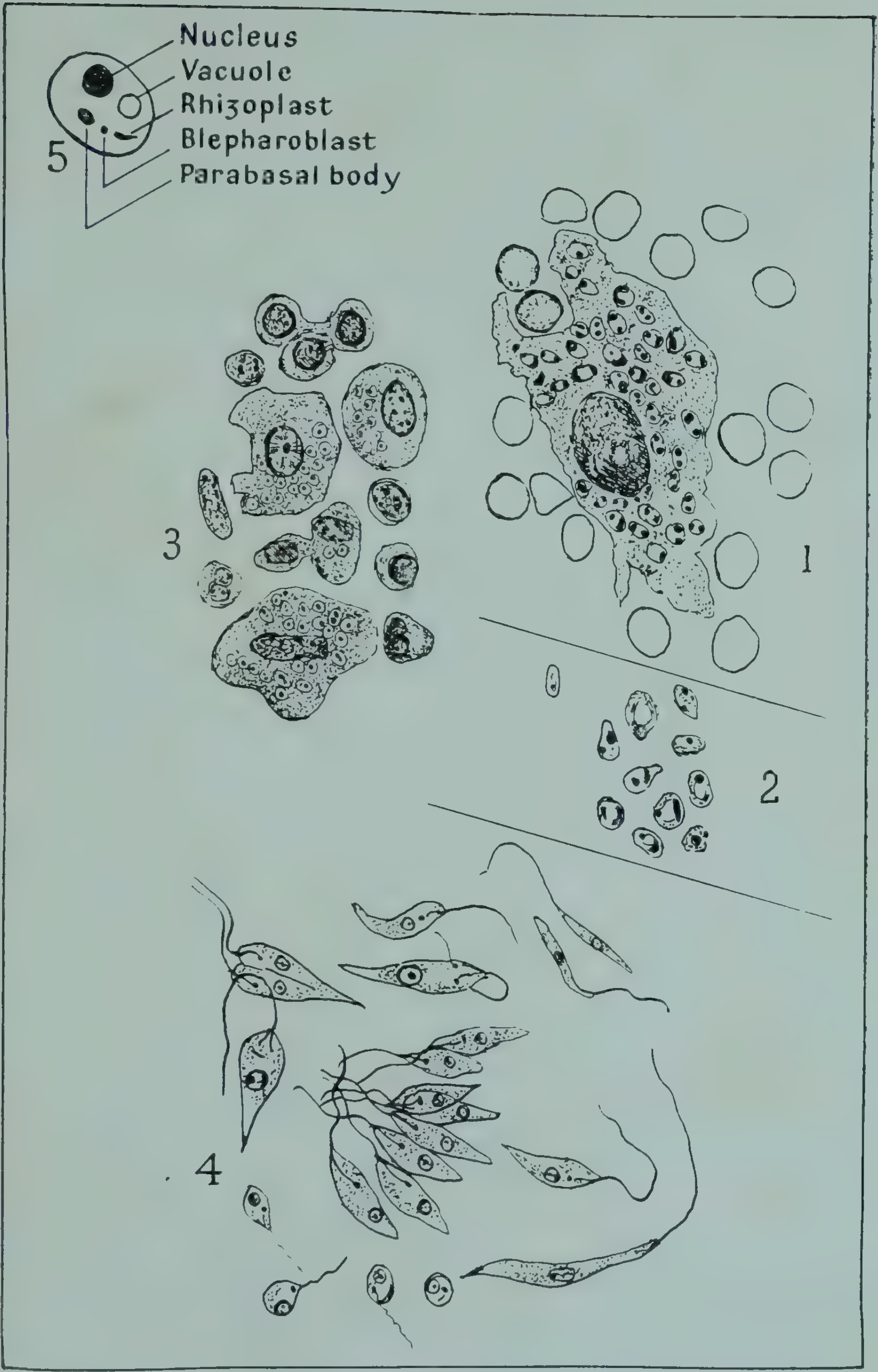

Nucleus
Vacuole
Rhizoplast
Blepharoblast
Parabasal body
5
3
1
2
4

Plate III. Leishman-Donovan bodies in Kala-azar and related forms.

ÆTIOLOGY

Leishmania—Leishman-Donovan body—an oval or round body 2–4 μ in diameter, cytoplasm enclosed in membrane, nucleus, vacuole, rod-shaped kinetoplast (parabasal body + blepharoplast), represents axoneme of future flagellum. Found in endothelial cells, histiocytes and clasmatocytes. Division by longitudinal fission, often in clumps or clusters ; sometimes 50–200 or more.

NOMENCLATURE.

Kala-azar : *Leishmania donovani.*
Oriental sore : *L. tropica.*
Infantile Kala-azar : *L. infantum.*
Espundia : *L. braziliensis.*
Canine Kala-azar : *L. caninum.*

CULTIVATION.—In blood media at 20–22° C., rapid multiplication, assume motile flagellated "*leptomonas*" form, 12–20 μ ; multiply by longitudinal fission. Subinoculation easy, into dogs, cats, monkeys, hamsters (*Cricetus*).

LIFE HISTORY.—Transmission through sandfly (*Phlebotomus*), essentially same as that of *Herpetomonas* or *Leptomonas.* In stomach, leishmania forms develop into typical elongated leptomonas, spread forward to proventriculus and buccal cavity ; elongated metacyclic forms attached to walls of pharynx forming obstructive masses (blocked sandflies) ; parasites injected by sandfly in act of biting.

SANDFLY TRANSMISSION.

1. **Leishmania—L. donovani** and **L. infantum.**

Russia (Far East): rural and urban types	*Phlebotomus arpaklensis.*
Mediterranean (Italy)	*P. perniciosus, P. macedonicus.*
Crete	*P. major.*
China	*P. sergenti* var *mongolicus* and *P. chinensis.*
Sudan	*P. orientalis.*
Kenya	*P. garnhami.*
India	*P. argentipes.*
Brazil	*P. intermedius.*

2. **L. tropica.**

N. Africa and E. Mediterranean	*P. papatasii.*
Italy	*P. macedonicus* (*perfiliewi*).
Iraq, India, Persia	*P. sergenti.*
Central Asia	*P. caucasicus.*
Takzikistan (E. Russia)	*P. arpaklensis.*

3. **L. braziliensis.**

Brazil, N. Argentine, Paraguay	*P. intermedius, P. longipalpis, P squamipes, P. migonei.*

A. KALA-AZAR (VISCERAL LEISHMANIASIS) "DUM-DUM" FEVER

Infective disease, resembling chronic malaria, with splenomegaly and hepatomegaly. Organism—*Leishmania donovani.* Infantile form in

PLATE IV

INTERMEDIARY HOSTS.

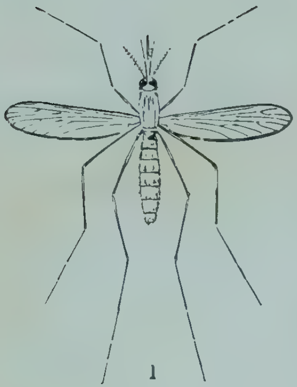
A.

1–4. *Anopheles maculipennis* (Malaria. *Wuchereria bancrofti*).

1.—Female.
2.—Resting position.
3.—Larva. Breathing position at surface of water.
4.—Egg.
(a, Under side ; b, Upper side).

5–8. *Culex fatigans* (*W. bancrofti*).

5.—Female.
6.—Resting position.
7.—Larva. Breathing position at surface of water.
8.—Egg raft.
9.—*Aëdes ægypti* (Yellow and Dengue Fevers). Female.



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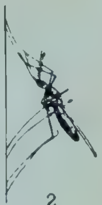

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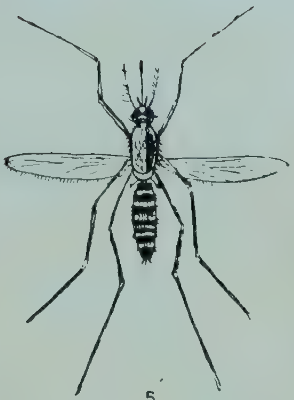

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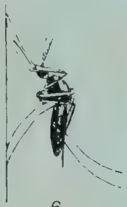

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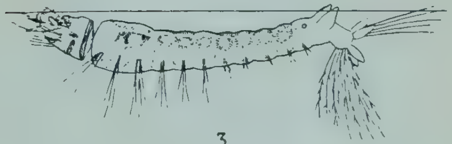

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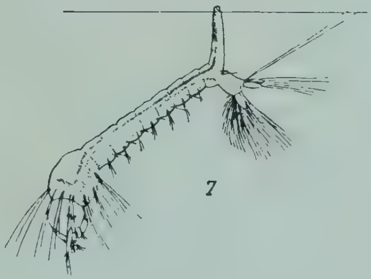

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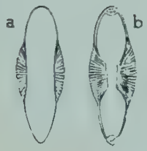

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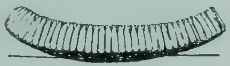

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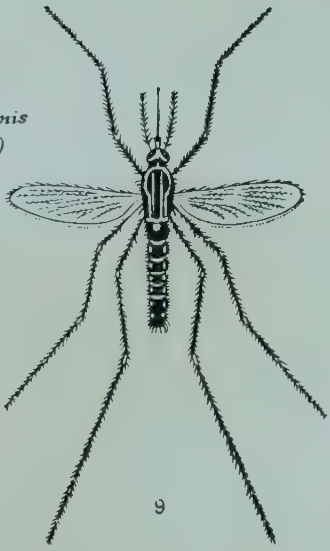
1–4. *Anopheles maculipennis*
(Malaria. Wuchereria bancrofti)

5–8. *Culex fatigans*
(W. bancrofti)



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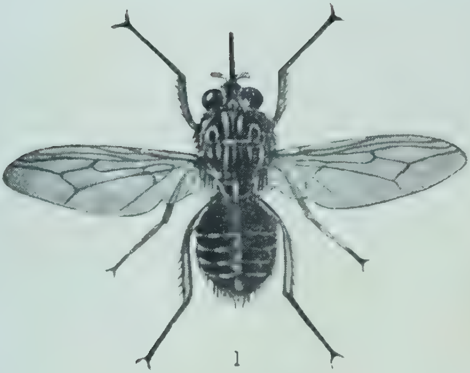
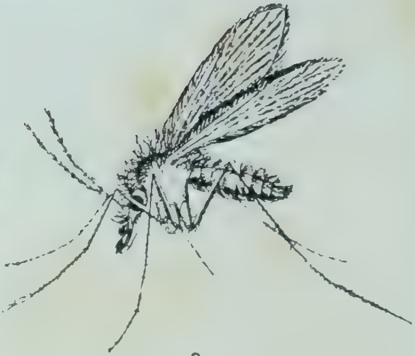
Aëdes aegypti
(Yellow and Dengue Fevers)

Plate IV. Intermediary Hosts.



1

Glossina palpalis



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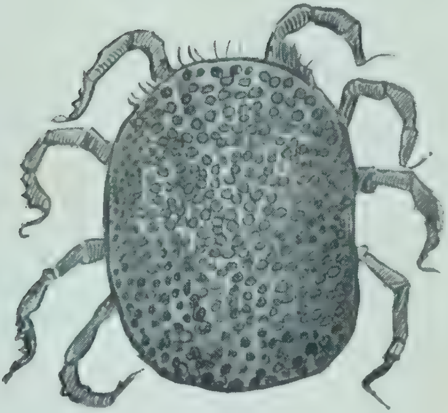
Phlebotomus papatasii



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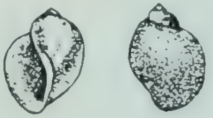
Ornithodorus moubata



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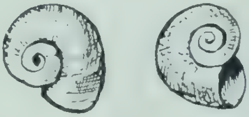
Bulinus contortus



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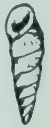
Planorbis boissyi



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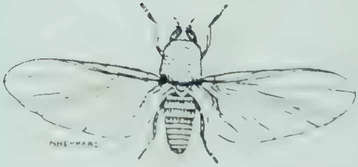
Oncomelania nosophora



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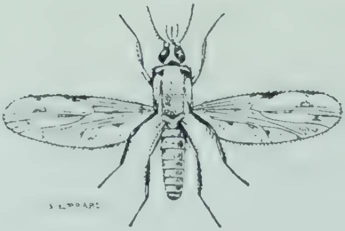
Simulium damnosum



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Culicoides austeni

Plate V. Intermediary Hosts.

PLATE V

INTERMEDIARY HOSTS.

B.

1.—*Glossina palpalis.* Tsetse. (*Trypanosoma gambiense*).

2.—*Phlebotomus papatassii.* Sandfly, female. (Sandfly Fever and Oriental Sore. *Leishmania tropica*).

3.—*Ornithodorus moubata.* Soft tick. (Relapsing Fever. *Spirochæta duttoni*).

4.—*Bulinus contortus.* Fresh-water snail. (Schistosomiasis—*Schistosoma* (*Bilharzia*) *hæmatobium*).

5.—*Planorbis* (*Biomphalaria*) *boissyi.* Fresh-water snail. (Schistosomiasis—*S. mansoni*).

6.—*Oncomelania nosophora.* Fresh-water snail. (Schistosomiasis—*S. japonicum*).

7.—*Simulium damnosum.* Buffalo gnat. (Onchocerciasis—*Onchocerca volvulus*).

8.—*Culicoides austeni.* Midge. (Filariasis—*Dipetalonema perstans*).

Mediterranean—*L. infantum*. Associated with similar disease in dogs—*L. caninum*. Parasites of the reticulo-endothelium.

Geographical distribution.—India, E. Coast (epidemic and severe), Assam, China, N. of Yangtse and in S. China (Canton), Transcaspia, Transcaucasia, Turkestan, S. Manchuria, S. Sudan, Italian Somaliland, W. Abyssinia, N. Kenya, Darfur, Chad Territory, French Guinea and Congo, Gambia, Nigeria (rare), Morocco, Tunis, Algeria, Persia, Saudi Arabia, Iraq and Egypt (rare), Brazil and Argentine. Infantile form, Mediterranean area, Italy, Sicily, Greece, Corsica, Malta, Aegean Islands, Portugal, S. Spain, Turkey, Yugoslavia, Palestine, Transjordania. Kala-azar reported from France (Cherbourg-Marseilles) and Hungary. In S. America widespread, at first supposed to be new parasite—*L. chagasi* (not accepted). Mexico, Venezuela, Colombia, N. Brazil, Bolivia, Paraguay.

Association with dogs and other animals.—Not invariable, usually in Mediterranean, especially in Sicily, Portugal and Turkestan, but canine leishmaniasis occurs in many areas, notably Iraq, where human disease is very rare. Also canine disease is not common in India and China, where dogs are not notably affected by it. Jackals suspected in subtropical regions of Far Eastern Soviet Russia during reclamation of Vakhsh Valley in Tadjikistan where K.A. is a typical zoönosis. In populated towns the disease has long been adapted to man whilst retaining its infectivity to dogs and is of the Mediterranean type with highest incidence among children. In rural districts it is highest among adults.

Transmission.—Through sandfly: in India, *Phlebotomus argentipes*. Final proof of transmission to man obtained by Christophers, Shortt and others. Transmission to hamsters (*Cricetus* and *Cricetulus*) also successful. Possibly direct transmission by personal contact *via* nasal secretion ; L.D. bodies are found in nasal mucus, also in urine (occasionally) and in fæces.

SANDFLY TRANSMISSION.

1. L.D. bodies undergo specific development in *Phlebotomus*.
2. When fly is infective cannot take blood meal without inoculating leptomonad forms. Infected sandflies bite voraciously : in *P. argentipes* the blockage of the œsophagus with developmental forms resembles fleas infected with *P. pestis* (*q.v.*) (see p. 86).
3. In *Phlebotomus* caught in K.A. houses leptomonads are found, apparently derived from L.D. bodies.
4. These forms are infective to hamsters (*Cricetulus*) by inoculation or by ingestion of flies.
5. Actual transmission has been proved by bite of infected sandflies to hamsters and also to man.

CONGENITAL TRANSMISSION of K.A. from mother to child recorded.

K.A. attacks both sexes, all ages, recently arrived immigrants most readily. In Mediterranean mostly attacks children aged 5 months to 10 years, but adults also ; in India it affects all ages.

PATHOLOGY

Body emaciated, abdomen swollen. **Spleen:** grossly enlarged, capsule thickened, nodular. Cartilaginous in chronic stages ; numerous infarctions. Congestion of splenic pulp ; one-fifth composed of parasites. **Liver:** enlarged, brown, mottled. Pressure atrophy of parenchyma and eventually fine intralobular cirrhosis. Parasites in Kupffer cells filled with parasites. **Gastro-intestinal tract:** proliferation of reticulo-endothelial cells, especially in duodenum and jejunum. Villi hypertrophied and swollen, packed with parasitized cells. **Lymphatic glands:** enlarged and congested. L.D. bodies +. Underlying essential pathology is blockage of reticulo-endothelium. Parasites, engulfed by endothelial cells, multiply until cell ruptures and organisms escape into blood stream and are carried to other organs.

CLINICAL PATHOLOGY

Progressive anæmia of secondary type, but when marrow is destroyed anæmia becomes of pernicious type. Not so marked in the infantile form. Usually 2½–4 million r.b.c. with corresponding reduction of hæmoglobin.

Leucocytes : Usually leucopenia
below 3,000 in 95 per cent. of cases.
" 2,000 " 73 " "
" 1,000 " 42 " "

$\frac{\text{wbc}}{\text{rbc}}$ normal $\frac{1}{750}$: K.A. $\frac{1}{1{,}500}$ or $\frac{1}{2{,}000}$ (Diagnostic)

Eosinophiles reduced. Relative increase in large mononuclears and lymphocytes. Auto-agglutination of r.b.c. (cold agglutinins) common, with diminished coagulability, diminished alkali reserve, euglobulin in serum. In terminal stage : bilirubinæmia and indirect Van den Bergh reaction +.

CLINICAL FEATURES

Incubation period varies—may be as short as ten days—usually unascertainable. (Kirk in Sudan 3–6 months.) Infection may lie latent for as long as 2½ years (Jopling). Onset gradual or sudden, with high fever, rigor, vomiting. Initial fever intermittent with double remissions (" double crisis "), sweating severe; duration 2–6 weeks. Waves of fever somewhat resemble undulant; daily rigors not uncommon. Splenomegaly +; hepatomegaly later. Slight lymphadenitis common in groins, but cervical glands involved in Chinese form. Intervals of apyrexia and improvement, finally low fever sets in. In Kenya special form with primary lesion on legs in goatherd boys at site of infective bite with lymphatic spread to regional glands and eventually to the viscera. Rheumatic pains in limbs. Amenorrhœa in women. Tongue clean, appetite good, but great emaciation of arms and legs; œdema ; ascites in terminal stages. Dusky pigmentation of hands and feet (" Black disease ") especially in Europeans. Trophic changes in hair, purpura, occasional bleeding from gums.

Gingivitis and stomatitis common. Spontaneous recovery possible. Acute and specially resistant cases in Sudan, N. Kenya and Mediterranean. Death may occur in four months. Frequent terminal complications: bacillary dysentery, tuberculosis, pneumonia, also K.A. dysentery due to L.D. bodies in intestines. Noma and cancrum oris now considered due to agranulocytosis, of which two kinds observed:—

1. Due to leishmania infection.
2. Due to antimony treatment.

Prognosis grave (see treatment).

Infantile K.A.—Onset insidious; splenomegaly, anæmia, general lymphadenitis. Has been confused with Banti's disease.

Dermal leishmanoid.—Dermal lesions noted in K.A.: ulceration, especially in Sudan (possibly combination of K.A. and O.S., but not usually found together)—rare in India. Also nodular diffuse papular eruption of face and trunk, often in antimony-treated patient (post-K.A. leishmaniasis). Lesions usually appear 2–3 years after signs of visceral infection have disappeared. **Xanthoma** type: orange-coloured plaques which do not ulcerate. Depigmented areas of skin frequently encountered on face and upper extremities. At first very small, they gradually enlarge to irregular areas, ½ in. in diameter. Nodules may replace depigmented patches. Often confused with leprosy.

Pathology: Histiocytes and clasmatocytes beneath epidermis containing parasites, not usually in large numbers.

DIAGNOSIS

Confused with chronic malaria: splenomegaly, irregular pyrexia, leucopenia from endemic zones suggest K.A.; quinine and other antimalarial drugs ineffective in reducing fever; L.D. bodies demonstrated by spleen, liver, sternal and lymph gland puncture. **Spleen puncture:** most satisfactory, but may be dangerous. Patient injected with 1/100 gr. (0·648 mgm.) of atropine and skin anæsthetized. Record syringe with dry barrel and No. 10 needle. Pulp extracted, expressed on clean slide and stained with Leishman's stain or Giemsa. L.D. bodies easily seen in splenic pulp cells. **Liver puncture:** same technique. Usual mistake is to take too much blood. L.D. bodies scantier than in spleen. **Sternal puncture:** with special puncture needle (Witts), L.D. bodies easily obtained, material suitable for culture on N.N.N. medium. Even in absence of parasites myelogram is distinctive: granulocytes 23, erythroblasts 24, hyaline leucocytes 53. (Normally granulocytes four times as numerous as erythroblasts and 3·5 times as numerous as hyaline leucocytes.) **Lymph gland puncture:** dry sterile hypodermic needle; No. 16, inserted into inguinal gland, steadied by finger and thumb; lymph massaged into lumen of needle into which it runs by capillary attraction, blown out on to slide and stained, but L.D. bodies not always found.

Blood examination.—In Assam L.D. bodies frequently found in large mononuclear cells in blood film; thick drop method necessary.

Also by centrifuging 5 c.c. of blood diluted in Locke's solution (sodi. chlor. 9 gm., pot. chlor. 0·4 gm., calc. chlor. 0·2 gm., sodi. cit. 10 gm., aq. dest. 1,000 c.c.) at 750 revolutions ; L.D. bodies in sediment.

Complement fixation test is performed with antigen prepared from spleen of heavily infected hamster. This antigen is still active after being powdered and dried.

Blood culture.—2 c.c. of blood mixed with 1 c.c. of 6 per cent. citrate solution in cool incubator, left for two hours, sediment inoculated into N.N.N. medium, incubated at 22° C.

Serum tests.—Aldehyde-formol-gel, or serum-formalin reaction, depends upon excess of euglobulin. 1 c.c. of clear serum in test tube, 3 by ½ in., add one drop of 30 per cent. formaldehyde, shake well, place in test-tube rack at room temperature. Solidification in 3–20 min. : opacity like white of egg is diagnostic. In some cases reaction does not become positive until advanced stage of disease. Plasma globulin 4, serum albumin 2·8 (normal 2·5 : 4).

Antimony test (Chopra).—Precipitation on addition of antimony compound (stiburea). Aldehyde and antimony tests of equal value.

DIFFERENTIAL DIAGNOSIS.—From chronic malaria (hepatomegaly more evident in K.A., also often œdema of legs) ; splenic anæmia; Egyptian splenomegaly (*Schistosoma mansoni*); chronic brucellosis (*Br. melitensis*); malignant endocarditis; leucocythæmia; visceral syphilis; lymphadenoma; tuberculosis of spleen; indigenous tropical hepatosplenomegaly (Fawdry); in China, Philippines and Japan from *Schistosomiasis japonica.*

Indigenous splenomegaly is described in S. Yemen—has been found in Aden Protectorate and in the Kavirondo and Wakemba in Uganda and Kenya. The degree of anæmia varies within wide limits. Zlotnick (1955) has described what appears to be a new protozoan parasite in the leucocytes. The illness commences with attacks of fever and rigors every five days.

TREATMENT

Antimony compounds. *Pentavalent preparations:* neostibosan, urea stibamine (stiburea, carbostibamine), antimosan (Fouadin), aminostiburea, solustibosan. Probably all of equal value. In adults given intravenously, by steppage doses on alternate days—0·1 gm. (1·5 gr.)—0·2 gm. (3 gr.)—0·3 gm. (4·5 gr.); total varies from 3–10 gm. (46–155 gr.), dissolved in 2–6 c.c. of distilled water (not boiled). Injections to be given slowly.

Antimony reaction: coughing, retching, vomiting. Overdosage : gastro-intestinal disturbance and diarrhœa, jaundice, arthritic pain, especially shoulder pain.

In children : intramuscular injections 0·1 gm. In infantile K.A. in Italy intravenous injections into jugular vein.

Action of antimony on L.D. bodies uncertain. No direct action *in vitro.* Some Mediterranean, Sudanese and Kenya types resist antimony treatment.

Diamidino-stilbene (Stilbamide, M. & B. 744).—Not metallic, contains NH_2 group. Therapeutic dose: 1 mgm. per kilo., intravenous, 8–10 injections on successive days of 45 mgm. (0·69 gr.) dissolved in 10 c.c. of distilled water; must be freshly prepared otherwise liable to develop toxic properties. Injected very slowly, to avoid vomiting, effects considerable fall in blood pressure, temporary decrease in blood-sugar, flushing of face, burning sensation in chest and abdomen—relieved by adrenaline. Full therapeutic effect not seen for 10–14 days, then shrinkage of liver and spleen, drop in pyrexia, increase in weight, increase of leucocytes. Has cured cases resisting antimony.

Disadvantages.—Neuropathies liable to ensue possibly from action on basal ganglia producing anæsthesia of head and neck. In some effects are transitory, sometimes permanent. Epileptiform seizures may ensue. Numbness of lips a feature.

Pentamidine now considered safer and more satisfactory in same dosages.

Splenectomy together with pentamidine injections has been successfully practised in very resistant cases.

After-treatment.—Agranulocytosis of K.A. does not respond to pentanucleotide, but to blood transfusion and injection of adrenaline ; anæmia responds to iron therapy. Spontaneous cure has been recorded.

PROPHYLAXIS

Destruction of K.A. dogs (reservoir host) effective in Sicily. Measures against sandfly (*Phlebotomus*), *e.g.*, removal of thatch on roofs and cementing floors. DDT residual spray, in particular, has proved lethal to sandflies in their haunts.

B. ORIENTAL SORE

Tropical sore, Delhi boil, cutaneous leishmaniasis, Aleppo boil. Specific ulcerating granuloma of skin with intial papule (later ulcer). Parasite : *L. tropica.*

GEOGRAPHICAL DISTRIBUTION AND EPIDEMIOLOGY

S. Italy, Sicily, Algeria, Tunis, Morocco, S. Greece and Crete, Cyprus, Egypt, Syria, Caucasus, Palestine (Jordan Valley), Transjordania, Iraq, Persia, Sudan, Arabia, N. Nigeria, India (N.W. Frontier, Quetta), Transcaspia, Turkestan, S. China (Hunan), West Indies, South and Central America (usually, but not invariably, with Es. : Peru, Bolivia, Brazil, Guianas), Mexico, West Indies. In tropics at beginning of cool season, in subtropics and Mediterranean at end of summer, early autumn. O.S. may occur in countries where K.A. is endemic, but has distinct distribution. O.S. in W. India. K.A. confined to E. coast. In N. Africa O.S. occurs N. of Lat. 35°; K.A. south. Persia and Iraq : O.S. very common, K.A. rare. In Central Asia O.S. and K.A. occur together. O.S. does not protect against K.A. or *vice versa*. In Iraq children contract O.S. at 2–3 years of age, immunity acquired;

everyone in Baghdad used to have scars of sores on face. O.S. found in animals, on ears and nose of cats and dogs (winter months), on gerbilles, brown bears and horses. Monkeys susceptible.

ÆTIOLOGY

L. tropica, indistinguishable from *L. donovani*, in large numbers at base and edges of sore, but most numerous in preliminary papule, spreads *via* lymphatics in which it forms secondary nodules and eventually secondary sores.

Cultivation.—On N.N.N. medium as for K.A. ; surface of sore sterilized with iodine, edge punctured with fine glass pipette, serum abstracted and inoculated into water of condensation of medium. Now penicillin and streptomycin added to prevent contamination. In intense infections flagellated parasites appear in 48 hours, in scanty not for 2–3 weeks.

Transmission.—Considerable proof that sandfly is sole agent in natural transmission (but can be artificially inoculated direct). Transmission experiments in Baghdad and Algiers successful (*P. papatasii*), monkeys and dogs experimentally inoculated. In Turkmenistan two types recognized—dry and moist. The former, or rural type, is said by Latyshev to be associated with gerbilles (*Palliosomys erythourus*) which constitute reservoir host.

In Tadjikistan a high proportion of the local *Phlebotomus arpaklensis* which breed in the gerbille burrows are infected with leptomonad forms of *Leishmania tropica*. In N.E. Persia a similar situation exists and the local gerbille there is *Rhombomys opimus*.

PATHOLOGY

Small round-cell infiltration of dermal and subdermal tissues in vicinity of blood vessels, lymphatics and sweat glands forming syncitium ; giant cells occasionally ; local necrosis ; *L. tropica* in numbers in macrophages or leucocytes, but, when parasites are scanty, structure resembles lupus. Numerous giant cells.

CLINICAL FEATURES

Incubation period very variable—few days or weeks to six months or longer. Febrile reaction may presage appearance and parts exposed to sandfly bites. At first small itching papule. Sores appear most commonly on face, arms and legs, later covered with dry crust from which serum exudes ; then ulcerate ; secondary sores may form on margins and coalesce to produce large, raw, ragged area. Granulation and healing gradually form pink cicatrix. Scar tissue may lead to deformity of neighbouring parts (epiphora, etc.). Sores may be multiple—as many as 100 on different parts—usually on face and hands ; also on forehead, cheeks, nose, lower lip, tip of ears (apt to be mistaken for lupus) and tongue (rare) ; sometimes on perineum and margin of anus. Initial papule may not ulcerate, but persists as limpet-like scaly excrescence—flattened plaque as in syphilis. Secondary infections may produce local cellulitis and, when ulcerated, regional lymphatic glands implicated. Associated subcutaneous nodules in course of lymphatics lead to spread of sores from primary focus. Verrucose non-ulcerating (granuloma), warty growths or papules on legs and ankles in Egypt. In S. Sudan, rarely in India, attacks mucous membrane of nose and lips. Query same as Espundia (*q.v.*) ? Lupus-like lesions may appear in healing sore of leishmanial origin (apple-jelly nodules) ; but may be also true lupus.

Leishmaniasis recidiva or metaleishmaniasis (Marchionini) may resemble erysipelas with " serviette " distribution, allergic manifestations resembling tuberculides. Chronic form with dried and fissured scabs resemble tertiary syphilis. Generalised non-ulcerating form covering whole body resembles tuberculoid leprosy, known generally as dermal leishmanoid.

DIAGNOSIS

Easy in papular stage when L.D. bodies numerous in scrapings, or by puncture of margin with glass pipette. When ulcerated and secondarily contaminated, parasites may be scanty. *L. tropica* to be distinguished from yeast cells frequently seen in ulcerations. In doubtful cases cultural method now much preferred.

DIFFERENTIAL DIAGNOSIS.—On clinical grounds to be differentiated from yaws, syphilis, leprosy lupus, ulcus tropicum, blastomycosis and veld sore.

TREATMENT

Response to treatment depends greatly on nutrition and resistance. Tendency to heal on removal from endemic area.

GENERAL MEASURES : (1) In multiple sores intravenous injections of **tartar emetic** are effective, but pentavalent compounds, *Neostibosan, Neostam,* are better. Steppage doses—1½ gr. (0·1 gm.) to 4½ gr. (0·3 gm.) alternate days, total dosage 3 gm.—combined with scraping of sores and antiseptic lotion. *Solustibosan* in oily solution intramuscularly advocated for leishmaniasis recidiva.

(2) **Antimony** not efficacious for sores on face, ears, nose and lips. Secondary infections respond to antiseptic lotion (Eusol), nitrate of mercury ointment, also sulphonamide powder.

Cignolin paint.	Cignolin	gr. iv	(0·25 gm.)
	Ichthyol	gr. viii	(0·51 gm.)
	Ol. cadini	min. xl	(2·46 c.c.)
	Benzol. rect.	℥ i	(29·5 c.c.)

painted daily, for 2–4 weeks, on sores, and surface lubricated with vaseline. Other ointments : **Pellidol** (Bayer) 2 per cent.—diacetylamine-azol-toluol ; and **Orisol** (berberine sulphate).

(3) **Injections** into base of sores cause irritation and tissue reaction. Orisol (berberine sulphate) 2 per cent., 2–3 c.c., is painful. Penicillin injections indicated in ulcerating form with secondary infections. Atebrin in 15 per cent. solution injected into nodules in early stages effective.

Indolent sores on nose require scraping and occasionally excision and plastic operation. X-ray application and carbon dioxide snow sometimes employed. *N.B.*—Cicatricial sores may require plastic operation in vicinity of eyes and mouth. Indolent tubercles may be lupus (but usually are not and *L. tropica* may be cultivated from them).

PROPHYLAXIS

In endemic areas general measures against sandflies : sandfly net (see p. 130), or cover head and shoulders with fine-mesh muslin. DDT most effective against phlebotomus by using 50–100 mgm. per sq. ft. of surface (1–2 quarts of 5 per cent. solution to 1,000 sq. ft.). The inside walls are sprayed from floor to ceiling, special attention being paid to corners. Wherever sandflies shelter or breed in association with humans, outside sprayings of walls and rubble heaps afford a degree of control. In Turkey prohibition of using cow dung for plastering walls eminently successful. Prohibit dogs with sores. Prophylactic inoculation of children practised in Baghdad, Persia and Turkestan with cultures of *L. tropica*. Sores develop after two to three months and protect against further infection.

C. ESPUNDIA

Leishmania americana, Bubas braziliana, naso-pharyngeal leishmaniasis. A form of leishmaniasis affecting mucous membrane of nose, mouth, palate and lips, causing great destruction and unsightly deformities.

GEOGRAPHICAL DISTRIBUTION AND EPIDEMIOLOGY

Argentine (to 30° S.), Paraguay, Brazil (Sao Paulo, Rio, Bahia), Peru (50–25° S.). Not above 2,000 ft. Heat and moisture necessary, especially in chicle (gum) forests in rainy season. Mexico (Yucatan), British Honduras, Martinique, Guatemala, Colombia, Guianas, Uruguay, Bolivia, Ecuador. Epidemic in Paraguay ; common in men. Rarely similar cases recorded in Sudan, Italy, India, China.

Possible reservoir hosts : dog, agouti (*Dasyprocta*). **ES**-like lesions produced in *Cercopithecus* monkey infected with *L. donovani*.

ÆTIOLOGY

L.D. body indistinguishable from type, cultural characteristics identical. *L. braziliensis*.

Transmission.—Sandfly; *P. intermedius*.

PATHOLOGY

Typical of epithelial proliferation—granular tissue with dense infiltration of round cells, plasma cells and frequently Langhan's giant cells. Usually only a few leishmania can be found.

DIAGNOSIS

As for *L. tropica* : biopsy, granulation tissue, smear preparations. Intradermal test of Montenegro. Cultures of *L. enriettii* of the guinea-pig are used for antigen. Injection of cultures of leishmania is of value.

DIFFERENTIAL DIAGNOSIS.—From yaws, syphilis, leprosy.

CLINICAL FEATURES

Characteristic **primary** sore—indistinguishable from oriental sore—heals. **Secondary** intractable ulceration of nose, spreading to lips, mouth and pharynx, with erosion and obstruction, involvement of lymphatic glands, and multiple sores over body as well. Death from secondary complications : *e.g.*, bronchopneumonia, syphilis, gangrene. Commonly affects ears (*Oreja de chicleros*). Sores affect leg, 30 ; head, 11 ; hand, 10 ; hip, 4 ; elbow, 4 ; trunk, 3 ; knee, 3 ; neck, 2 ; buccal mucosa, 2 ; arm, 1 (per cent.). Atrophic form characterized by dry mucosa and formation of crusts which block respiration. Laryngeal lesions produce hoarseness, cough and dyspnœa.

TREATMENT

For generalized sores : pentavalent antimony (not effective in buccal lesions). Trivalent antimony (Fouadin-antimosan) much used ; intramuscular dose, 0·5–5 c.c., 20–30 injections, combined with local antiseptic applications such as sulphonamide paste, anthiomaline (see p. 197) also recommended. Streptomycin and thiazamid are used as adjuvants. Atebrin (mepacrine hydrochloride) recently recommended, injected into base of sores: 5 c.c. of 10 per cent. solution, together with 1 tablet (0·1 gm.) t.d.s. by mouth for seven days. Spontaneous cure sometimes.

PROPHYLAXIS

Reports from the State of Rio de Janeiro show that DDT residual sprayings play a great part in the elimination of this disease, as the insecticide is lethal to sandflies.

AFRICAN TRYPANOSOMIASIS

Acute disease produced by blood protozoan—*Trypanosoma*. Characterized by fever, adenitis, rash and eventually invasion of C.N.S. (sleeping sickness) ; conveyed by tsetse flies—*Glossina*.

Two varieties recognized in man—*T. gambiense* and *T. rhodesiense*. Former transmitted by *G. palpalis; G. tachinoides*, and latter by *G. morsitans*.

GEOGRAPHICAL DISTRIBUTION

Corresponds with that of tsetse flies concerned.

T. gambiense: W. Africa, Gambia, Sierra Leone, Gold Coast, Nigeria, Congo, S. Sudan, Uganda. In S. Africa new focus : Ngamiland vector, *G. palpalis;* in Ghana and N. Nigeria: *Glossina tachinoides*.

T. rhodesiense: Nyasaland, N.E. Rhodesia, S.E. Tanganyika, Portuguese E. Africa. Vector : *G. morsitans*, also, occasionally, *G. swynnertoni*. Associated with big game.

ÆTIOLOGY

T. gambiense and *T. rhodesiense* cannot be differentiated by morphology ; former adapted to man : latter principally parasite of antelopes. Status still uncertain.

Trypanosome elongated, with slender body, pointed anterior end, blunted posterior, central nucleus, marginal undulating membrane, terminating anteriorly in flagellum, swims with flagellar end foremost. Kinetoplast (blepharoplast) posterior to nucleus near posterior extremity. Multiplies by binary fission. Parasite of blood plasma: in terminal stages invades solid organs, especially brain.

Development in tsetse: cyclical in stomach, metacyclic forms spreading forward to proboscis and salivary glands. Cycle depends on temperature, usually 18 days. Infection conveyed by bite. Eight per cent. of wild flies (both sexes) infected. *Peritrophic membrane:* cylindrical tube suspended in intestine; up to 4th day trypanosomes are in lumen of the membrane: escape from posterior end, passing outside it to proventriculus. Direct mechanical transmission by blood on proboscis of Glossina is probably responsible for some epidemics.

Congenital trypanosomiasis: as in malaria and kala-azar congenital transmission may take place.

Cultivation: on blood media, frequent subinoculation.

Reservoir hosts. In laboratory : domestic and wild animals, especially antelopes. In nature : Speke's antelope (*Limnotragus spekei*), carrier of *T. gambiense* ; waterbuck (*Cobus ellipsiprymnus*) ; reedbuck (*Cervicapra arundinum*) ; duikerbuck (*Cephalopus grimmi*); and other antelopes normally harbouring *T. rhodesiense.* Wild animals show no signs of disease.

PATHOLOGY

Analogy with *Sp. pallida.* Chief lesions in C.N.S. and enlargement-hyperplasia of lymphatic glands ; proliferation of lymphocytes and reticulo-endothelium ; *T. gambiense* in lymph spaces of connective tissues and glands.

Brain: no gross lesions. Leptomeningitis in Virchow-Robin space and choroid plexus ; flattening of sulci ; extends vertically half-way down hemispheres. Spinal canal may be blocked by cell proliferation.

Blood vessels : infiltration (perivascular cuff) ; large distended " morula cells," " Marshalko cells "—degenerated plasmocytes. Lumen of vessel contracted; walls thickened.

C.S.F.: increased pressure and proteins ; cells 15–500 per c.mm. (lymphocytes, mononuclears, morula cells, eosinophiles and trypanosomes). In advanced cases, trypanosomes in brain tissue—frontal lobe, pons, medulla—aggregated into masses without relation to blood vessels. Trypanosomes enter canal from choroidal plexus.

Eyes: interstitial keratitis, optic atrophy occasionally.

Other organs: toxic changes ; hæmorrhages and ecchymoses.

T. rhodesiense sleeping sickness: similar, but more acute changes as a rule. Massive effusions into pleural, peritoneal and pericardial cavities, and inflammation of myocardium. Although C.S.F.

contains numerous trypanosomes, brain changes are not so advanced as in chronic *T. gambiense*. Probably visceral changes are fatal before C.N.S. gets involved.

CLINICAL PATHOLOGY

Blood: definite anæmia from toxins, corresponding diminution in hæmoglobin; colour index low; auto-agglutination of red cells; moderate leucopenia (bone marrow); large mononuclears relatively increased; increased serum globulin; alkali reserve diminished; blood sugar low.

CLINICAL FEATURES

Incubation period 2–3 weeks. Infective bite may cause local reaction.

STAGE I. "*Trypanosome chancre*": red discoloured nodule surrounded by œdema. Trypanosomes multiply in tissues; lesion visible for several months; trypanosomes in blood 3 weeks later, more numerous during pyrexia. Rigor fever like malaria; T. 99–106° F. (37·5–41° C.). Hyperæsthesia of periosteum of ulna (Kerandel's sign). Intense temporal headache. Tachycardia. Enlargement of lymphatic glands—sometimes universal—usually posterior cervical group (Winterbottom's sign), sometimes painful and tender. Insomnia; lack of concentration; fine tremors of lips and hands. Splenomegaly usual. Local œdemas: face (subocular), neck, lower abdomen, penis.

Rash.—Fugitive, erythematous, macular (like erythema multiforme), usually on chest, back, upper abdomen; may resemble erythema nodosum; may be confined to ring on shoulder. Brought out by heat (hot-bath). Later xeroderma and pruritus, neuralgic pain and paræsthesiæ. Recurrent orchitis (occasionally); periostitis of tibia (rare).

Eyes.—Toxic irido-cyclitis, choroiditis, optic atrophy (rare).

Death may occur from convulsions, status epilepticus, coma, or intercurrent disease.

STAGE II. *Sleeping Sickness* (cerebral trypanosomiasis). Usually chronic: 4–8 months, rarely 3 years. Sometimes latent period of 7 years may elapse between I and II.

Debility, languor, lack of concentration, loss of higher cerebration. Slow shuffling gait, vacant, mask-like expression, drooping of lower lip. Puffiness and drooping of eyelids. Stupor, somnolence in day: restlessness at night. Dull headache. Animal-like habits, behaviour often maniacal. Muscular fibrillation, tremor of hands and tongue.

Then bed-ridden, apathy; gross tremors of tongue, facial muscles and hands—anorexia; torpor; deafness. Sleeping with unmasticated food in mouth; wasting. Epileptiform convulsions with temporary pareses; occasionally meningism. Intolerable pruritus of skin, bed sores, swelling of lips.

Finally, incontinence, coma, death.

Symptoms sometimes not unlike G.P.I. Reflexes at first exaggerated, then absent. Urine normal; bowels constipated.

Clinical categories in natives :—

1. Mild—few symptoms—equilibrium between host and parasite.
2. Chronic sleeping sickness—commonest.
3. Acute—leading to death from toxæmia in some epidemics (in Tanganyika predominates).

Complications and sequelæ.—In Europeans recovering from trypanosomiasis cerebration may be temporarily disturbed.

In natives complications aggravate and mask disease : malaria, ancylostomiasis, schistosomiasis, septic rhinitis, otitis media. Starvation, dysentery and pneumonia frequently terminal.

Mortality.—Spontaneous recovery often. When sleeping sickness stage is well advanced death is inevitable, even with modern therapy. Whole populations in Central Africa formerly wiped out.

Immunity.—When disease has lasted long time, immunity is acquired (as in wild animals to appropriate trypanosomes). No evidence that immunity in individual is easily acquired. Disease more acute in European than in native (usually).

DIAGNOSIS

Blood examination, stained by Leishman, examined with low-power $\frac{1}{6}$ lens. Thick films often useful. Centrifuge citrated blood. Auto-agglutination of r.b.c. (cold agglutinins) ; relative leucopenia ; increase of large mononuclears.

Animal inoculation : rat or monkey (*Macaca*, *Cercopithecus* best). Blood and lymph culture on appropriate media (Razgha's medium and N.N.N.).

Lymph gland puncture, with 16-size hypodermic needle, massaging gland (see p. 26). Successful in 87 per cent.

Sternal puncture recently recommended.

Lumbar puncture.—C.S.F. for trypanosomes and cell changes.

Complement-fixation.—Antigen prepared from rats infected with *T. equiperdum* injected with ephedrine gives at least 10 per cent. more positive diagnoses than any other method.

On clinical signs.—Differentiation from malaria, kala-azar, syphilis, pellagra, leprosy, lymphadenoma (Pel-Ebstein). In later stages, from G.P.I., cerebral tumours, encephalitis lethargica, cerebral syphilis. (N.B.—Serum of uncomplicated trypanosomiasis may give pseudopositive W.R.)

TREATMENT

Two main drugs : Bayer 205 and tryparsamide.

"**Bayer 205.**"—Germanin, antrypol (British), moranyl (French), belganyl (Belgian). Complicated synthetic dye, extirpates infection in early stages (blood invasion). Chemotherapeutic index high, *i.e.*, *dosis tolerata* is 160 times *dosis therapeutica*. Intravenous injection 1 gm. (15·4 gr.) in 10 c.c. distilled water. Total for cure

10 gm. (154 gr.). 1 gm. on 1st, 3rd, 10th and 13th days; thereafter at weekly intervals. *Intramuscular* less satisfactory; *intrathecal* contra-indicated.

TOXIC EFFECTS.—Drug cumulative, excreted in urine, causing albumin and granular casts, but no permanent injury. May cause toxic dermatitis.

Tryparsamide—arsenical—sodium salt of N. phenylglycineamide-*p*-arsonate. Similar preparations: tryparsanyl, etharsanol, proparsanol, neocryl, mapharsen, orsanine (French). Given intramuscularly or intravenously—latter satisfactory. Enters cerebrospinal fluid, therefore useful in sleeping sickness stage. Chemotherapeutic index low (ratio between curative and maximum tolerated dose) 1 : 2.

Large dosage 1–4 gm. (15·4–61·6 gr.). In average case, 1 gm. (15·4 gr.) in 10 c.c. distilled water (alkaline), subsequently 2 gm. (30·8 gr.) three times weekly. Total dosage 24 gm. (369·6 gr.). In chronic cases, up to 80 gm. (1,232 gr.). In advanced cases, 0·02 gm. per kilo.; on 4th day: 0·03 gm., on 8th day: 0·04 gm. per kilo.—course of 20 injections.

TOXIC EFFECTS.—Neuritis occasionally (optic neuritis most dangerous), optic atrophy. Treatment must be controlled by charting fields of vision (perimeter). Premonitory signs: photophobia, lachrymation, pain.

Evidence of cure: physical improvement and normal C.S.F. absence of albumin and cells.

Synergic.—Combined treatment now advocated. Preliminary injections of antrypol (Bayer 205), 1–3 (1 gm.—15·4 gr.—each) followed by 12 of tryparsamide (20–24 gm.—308–396·6 gr.) or alternating treatments. (Now used in Belgian Congo, Tanganyika, Nyasaland, Uganda.)

Melarsen B (Freidheim)=arsobal (France and Portugal). (B=BAL.) 3·6 per cent. sol. 4 mgm. per kg. Non-toxic in moderate doses. By mouth 150 mgm. and intravenously 25 mgm. Effective in second stage cases in three doses in weekly injections. Much used in French and Portuguese West Africa. No other drug has produced such good results in advanced *T. rhodesiense* cases.

Other drugs.—4 : 4′ diamidino-stilbene (stilbamidine), synthetic non-metallic compound, causes reduction of blood sugar. Tolerated dose 30 times minimum curative dose (see p. 28).

Pentamidine isethionate rated superior to stilbamidine. Intramuscular daily injections for 18 days. Doses from 1·6 to 5·15 mg. per kg. Intravenous 2 mg. per kg. Injection made slowly. Polyneuritis may ensue. Pentamidine recommended for mass treatments.

PROPHYLAXIS

Tsetse flies—*Glossinae*, more than twenty species known, confined to Central Africa and S.W. Arabia—are sombre-coloured insects, 6–13·5 mm. long, somewhat resembling, but bigger than, stable flies

(*Stomoxys*), but with thick proboscis projecting horizontally, large wings overlap like scissor blades. They are long with the 4th longitudinal vein curved sharply forward to meet short transverse vein at right angles. In some species abdomen marked by well-defined brown bands, interrupted in mid line. In *males:* beneath end of abdomen external genitalia form knob-like protuberance; sexes easily determined. Both sexes feed voraciously on blood. Proboscis in 3 parts—*labrum, hypopharynx, labium. G. palpalis* and *G. morsitans* active and feed all day from one hour after sunrise onwards. One species, *G. brevipalpis*, bites only after dark. Glossina bite usually painless, but may strike nerve-ending. Proboscis plunged to back of bulb, then withdrawn a little, and sucking proceeds. Bulb contains muscles activating cutting mechanism at tip of proboscis.

Life history.—Pupiparous ; larvæ mature one at a time within abdomen. Egg hatches, larva nourished by secretion from milk glands ; reaches uterus in 10 days. Larva deposited by female, ½ in. into loose soil or sand, or beneath leaves or logs. Pupa hardens and darkens. Pupal stage 3–4 weeks. Adult lives 3–6 months, produces 6–12 larvæ. *G. palpalis, G. tachinoides* (smallest), *G. morsitans* (most important).

G. palpalis.—Gambia, Niger, Benue and Congo rivers at 28° C. Constant high humidity and fairly heavy shade necessary ; not found in dense virgin raw forest. Range varies in different seasons according to food supply. Primary foci in dry : secondary in rainy seasons. Always in vicinity of water. Feeds on game-birds, monitors, lizards, crocodiles, domestic animals, man. Closely associated with latter. Maintained on human blood, but can subsist on crocodiles. Follows many objects : cars, bicycles, boats. Pupates in green places, never more than 20 yards from water, on dry bank, shaded from sun.

G. tachinoides never closely associated with man. Feeds largely on game. Puparia in dry sandy soil or shade near water. Very important relation to trypanosomiasis, especially virulent form in N. Nigeria.

G. swynnertoni is locally distributed in Tanganyika and parts of Kenya, and is an important vector for *T. rhodesiense* and for trypanosomes of cattle. It transmits trypanosomiasis to man at Mwanza, L. Victorian. It is a game feeder.

G. morsitans conveys trypanosomes of wild game and domestic animals, especially *T. brucei* of antelopes and *T. rhodesiense* (similar to *T. brucei*) of man. Distribution in W. Africa corresponds to *G. palpalis*, but more extensive. In Nyasaland occurs beyond range of latter. S. limit is Zululand. Habits different : never flies with *G. palpalis*, open country, more resistant to dry conditions, therefore wider range. In dry season throughout E. Africa in Savannah (bush) country at all seasons, but in W. Africa is forced back to primary foci in dry season. Feeds largely on man or any living animals ; particularly associated with game, not dependent on human blood. Concentration varies with distribution of game ; " fly belts " therefore variable. Puparia in dry, friable earth—in E. Africa under fallen logs, placed so as to catch morning sun. (*See* P. A. Buxton, " The Natural History of Tsetse Flies," 1955.)

PROPHYLAXIS OF TRYPANOSOMIASIS

Based on bionomics of tsetse flies. Avoidance of " fly belts." *G. palpalis* belt is usually narrow strip of bush on water's edge—range beyond one mile.

I. MEASURES CONCERNING MAN

Early diagnosis and treatment of infected individuals.

Mass injection of natives with arsenicals—tryparsamide (Congo)—lowers index of new infections : objection : arsenic-fastness rapidly acquired by trypanosome, and then acquired character transmitted through Glossina (Yorke).

Prevent contact between man and fly by mass movement of infected population to fly-free area (as in Sesse Islands of Lake Victoria 50 years ago).

Clear bush along lines of communication round houses, ferries, wells, roads. Segregation of big game into game reserves for *G. morsitans*. Fly follows big game.

II. MEASURES CONCERNING FLY

(*a*) **Fly itself.**—Trapping and catching by hand. Training " fly boys." Fly paper or tanglefoot on clothes and wooden shields on backs of natives, or on screens. Glossina extirpated on isolated islands, *e.g.*, Principe in Bight of Benin. Respond to moving objects, bicycles, or motor-cycles, and can thus be caught.

Fly traps.—Harris' most effective against Glossina, especially *G. palpalis*. Consists of light canvas trap as big as and roughly resembling cow. Full trap 1–200 flies daily, especially in Zululand ; not so successful against *G. morsitans*.

(*b*) **Haunts of fly.**—Clearing only effective if constantly renewed in bush country ; causes soil erosion. More successful for *G. palpalis* than *G. morsitans*. Form artificial breeding places by piled-up logs, properly supervised, where pupæ are collected and destroyed. DDT action on tsetse flies not yet worked out. Five per cent. solution in kerosene sprayed on " screens " and on cattle is lethal and deters flies from probing, whilst solution leaves behind crystals which are rubbed off, but 1 per cent. solution in kerosene emulsified with an equal quantity of 5 per cent. gum is most effective especially against *G. pallidipes, morsitans* and *swynnertoni*. Spraying of DDT by aeroplanes, using finely atomized spray, has been proved effective in limited areas in Zululand. Twenty per cent. solution dissolved in four parts of toluene oil and seven parts of C.I. fuel oil. At speed of 120 m.p.h. aircraft covered 50 acres per mile with swathe width of 70 yards. Sprayed 3 times in 5 weeks allowing for normal gestation period of flies. Total eradication not achieved, but reduced to low level. Poison Bait cattle sprayed twice weekly with DDT have been used to reduce numbers of *G. morsitans* and *G. swynnertoni* with success in N. Tanganyika.

Chemoprophylaxis.—Prophylactic injection of " Bayer 205 " (antrypol) 1 gm. (15·4 gr.) does not prevent infection, but mitigates pathogenicity of trypanosome. Relative protection lasts 3 months. Has been tried extensively in Belgian Congo. Pentamidine prophylaxis also employed—injections 4 mgm. per kg. body-weight at intervals of six months. Incidence reduced to $\frac{1}{13}$ of former figure. Antrypol injections combined with this drug inhibit some of the toxic effects.

Antrycide chloride destroys *T. rhodesiense* in doses of 25 mg. per kg., and when injected subcutaneously, possesses marked prophylactic properties. It is specially suitable for cattle and other animals which may serve as " reservoir " hosts.

S. AMERICAN TRYPANOSOMIASIS. CHAGAS' DISEASE

Acute and chronic ; caused by *Trypanosoma cruzi*, disseminated by winged bugs (*Reduviidæ*). Lymphadenitis, splenomegaly.

GEOGRAPHICAL DISTRIBUTION

Brazil, W. Argentine, Panama, Guatemala, Bolivia, Peru, Uruguay, San Salvador, Venezuela, Ecuador, Mexico, Colombia.

ÆTIOLOGY

T. cruzi small " C "-shaped, scanty in blood, more abundant in children. Sometimes referred to genus *Schizotrypanum*. Proliferates by schizogony in internal organs and in striated muscle fibres, especially cardiac ; rapid multiplication, formation of leishmania nests, later trypanosomes ; these invade bloodstream and form broad and slender forms. Easily cultured on blood medium.

Life history.—Development in bug. Trypanosomes ingested by *Panstrongylus megistus* and allied species, pass through many stages in intestinal tract, 8–10 days ; fully-formed *metacyclic* forms re-appear in hindgut, pass out through fæces. Infection by defæcation into wound caused by bite. Transmission in bug also hereditary. Development in larval, nymphal or adult stage of insect is so readily observed that method is used for diagnosis (*Xenodiagnosis*). Under natural conditions domestic cat is infected ; all laboratory animals susceptible. Congenital transmission may occasionally occur in man.

In Brazil bug is *Panstrongylus megistus*, " Barbeiro " ; in N. Argentine, *Triatoma infestans* ; in Uruguay, *T. rubrivaria* ; but other species of *Panstrongylus*, *Rhodnius*, *Eratyrus* and *Triatoma* can also serve.

Reservoir hosts.—Numerous ; list grows yearly. Mainly armadilloes, where burrows harbour bugs ; also opossum ; occasionally wild dogs, cats, weasels and bats.

T. rangeli pear-shaped, elongated trypanosome with small blepharoplast and attenuated tail, first found in *Rhodnius prolixus* in Venezuela, Guatemala, Uruguay and Colombia. Is responsible for a number of human cases. Scanty in blood. Diagnosis is best effected by xenodiagnosis. Closely allied species *T. ariarii* measuring 31 μ recently reported in *R. prolixus* and causes human infections.

Congenital transmission of *T. cruzi* may occur. There is a real danger of transmission by *blood transfusion.*

PATHOLOGY

Heart enlarged ; pericardial effusion ; myocarditis ; infiltration by lymphocytes, plasmocytes and histiocyctes. Splenomegaly, parenchymatous degeneration of liver and general lymphadenitis. Serous effusions and subcutaneous œdema ; sub-serous ecchymoses, hæmorrhages into brain and spinal cord. Changes in voluntary muscles similar to those of heart : cyst-like swellings packed with leishmania forms of *T. cruzi.* Adrenals can be invaded.

Clinical pathology.—In acute stages : high leucocytosis with mononuclear increase ; severe anæmia uncommon.

CLINICAL FEATURES

Site of local inoculation swelling forms "Chagoma," and subsequently metastatic hæmatogenous tumours. Clinical picture very confused—varied accounts—but myxœdema and hyperthyroidism may occur. Myocarditis and sudden death are now being more frequently reported in men about 40 years of age. Electrocardiograms abnormal in 15 per cent. (RBBB, A-V blocks, ventricular premature contractions). Cardiomegaly with gallop rhythm. Unilateral conjunctivitis with œdema (Romaña's sign) distinctive, due to entrance of trypanosomes through conjunctiva (produced experimentally).

Incubation period uncertain, probably a month or longer. Usually pyrexia, but many cases symptomless. Erythematous well-defined rash on chest and abdomen occasionally.

Acute form.—Pyrexia, T. 104° F. (40° C.). Œdema of face. General adenitis, thyroiditis. Liver and spleen enlarged. Death from myocarditis.

Chronic.—Myxœdematous, cardiac and nervous forms described. Megacolon and megaœsophagus reported as sequelæ due to destruction of Auerbach's plexus by nests of leishmania forms, and rupture of pseudo-cysts, achalasia of the cardiac sphincter and consequent hypertrophy and dilatation of œsophagus = *Mal de Engasco* (the suffocating disease).

DIAGNOSIS

"C"-shaped trypanosome, scanty in blood, rare in C.S.F. Centrifuge blood. Animal inoculation (guinea pig) successful in acute: negative in chronic, form. Complement-fixation reaction (Machado)—antigen made from glycerin extract of heart and spleen of infected animals, or from cultures. *Intradermal* test with "cruzin." Xenodiagnosis (Brumpt): feed laboratory-bred *Panstrongylus* on suspected blood; cyclical development demonstrated.

Differential diagnosis.—From kala-azar in S. America.

TREATMENT

Antrypol arsenical and antimony compounds useless. Achromycin (tetracycline) in combination with primaquine, has recently given some encouraging results. Puromycin, as distinct from achromycin, also used (p. 256).

PROPHYLAXIS

Reduviid Bugs.—Large, conspicuous, gaily marked (red and black mostly), 3 cm. or less in length, live on wild animals in nests and burrows; certain species on domesticated animals. Sexes similar, but males on whole smaller. When engorged with blood after feeding, void white fluid from cloaca into bite. Female lays eggs singly; on emerging, larvæ engorge themselves with blood on four occasions and then moult, become nymphs, and finally moult a fifth time to become adult. Nymphs wingless; adults can fly. Whole cycle is 3–4 months.

Measures against bug.—Suppression of breeding places, and avoidance of reduviid bugs. DDT on whole successful, but nymphal instars resistant. Only found in grass native huts, pigsties, etc. Habits nocturnal; mosquito nets effective. Habitations placed at distance from armadillo burrows, and floors cemented to prevent armadillo burrowing. Insects also found in burrows of rock cavy (*Xerodon rupestris*). Wide measures now undertaken in Brazil by health authorities with residual sprays of BHC (gammexane), especially in houses and outbuildings. Two applications at intervals of six months has resulted in reduction of the incidence of the disease. Probably more effective than DDT.

AMŒBIASIS

Infection with protozoan—*Entamœba histolytica*—which is parasite of man, also of sewer rat and monkey. Though mainly in intestinal tract, may invade other organs and produce metastases. Disease therefore divisible into (*a*) *Primary or intestinal amœbiasis*, (*b*) *Secondary or metastatic amœbiasis*, of which the principal is hepatic amœbiasis.

GEOGRAPHICAL DISTRIBUTION AND EPIDEMIOLOGY

A. **Primary amœbiasis,** formerly considered disease of the tropics; by no means invariable. Found in greater or lesser degree in most countries, including N. Europe and U.S.A. Incidence probably correlated with bad sanitation. Specially prevalent in India, Indo-China, China, Philippines, N. and Central Africa, South U.S.A., Central and South America, West Indies. (Extensive outbreak in Chicago in 1933.) Sporadic outbreaks usually (as in

Chicago) water-borne, but may be fly-borne. In tropics commonly (as in China) conveyed by vegetables grown by native cultivators. Any age affected: most often adults; rarer in small children, especially Europeans under five, but may occur in infants where there is gross lack of sanitation. Some races especially susceptible, as in the Bantu tribes, and in Zulus in Natal where small children are attacked. In most countries men are more liable than women. House infection: insanitary habits promote spread as in Liverpool outbreak (Adams). In Britain and in N. Europe generally, where the infection is present on a small scale, clinical cases of any degree of severity are rare, but it has recently been recorded in a high proportion of mentally defective children in the London area.

Secondary amœbiasis, especially amœbic abscess of liver, very rare in children.

Mnemonic: transmission—"fæces, flies, fingers, food."

ÆTIOLOGY

Entamœba histolytica occurs in three main phases in the intestine, submucosa, mucosa and fæces.

(*a*) **Active or vegetative forms** (trophozoites) generally observed in bloody and mucous fæces. Tissue-invading form, causing ulceration of large intestine: clear, faintly greenish, transparent, 20–30 μ in diameter. When active, ejects hyaline pseudopodia, moves like "slug at express speed" with flowing or gliding movement. Outer clear ectoplasm; inner granular endoplasm. Ingests by pseudopodia r.b.c., leucocytes and tissue particles. Fluid absorbed by osmosis. Multiplies by binary fission; *nucleus* hardly visible in living state, consists of outer beaded chromatin ring with central karyosome (characteristic). In fæces often occurs in clumps or masses. Lives only few hours outside the body. Movements facilitated by warm stage. Degenerated individuals contain vacuoles. To see fine points of structure staining methods necessary. Small races of *E. histolytica* recognized.

(*b*) **Precystic forms** derived from tissue-invading individuals or from metacystic individuals. Active amœbæ divide, give rise to smaller individuals, which expel all food-particles and cease to feed. Rounded, small (5–20 μ), with sluggish movements, cytoplasm devoid of vacuoles and no ingested r.b.c. They are smaller than the lumen (*minuta*) form. Precystic amœba rounds up and secretes a thin membrane or cyst wall.

(*c*) **Cysts,** round, circular, in fæces and bowel lumen, not in ulcers or metastatic lesions. Vary in size, some races 7–9 μ, others 15–20 μ. Nucleus divides by fission into two, then four. Quadrinucleate cyst characteristic; nuclei retain distinctive character. Usually contain refractile *chromatoid bodies* and iodine-staining glycogen mass, sometimes seen in precystic. Do not hatch in intestine, nor develop further in fæces; remain viable 10 days or longer. After passing through stomach (cyst wall insoluble in

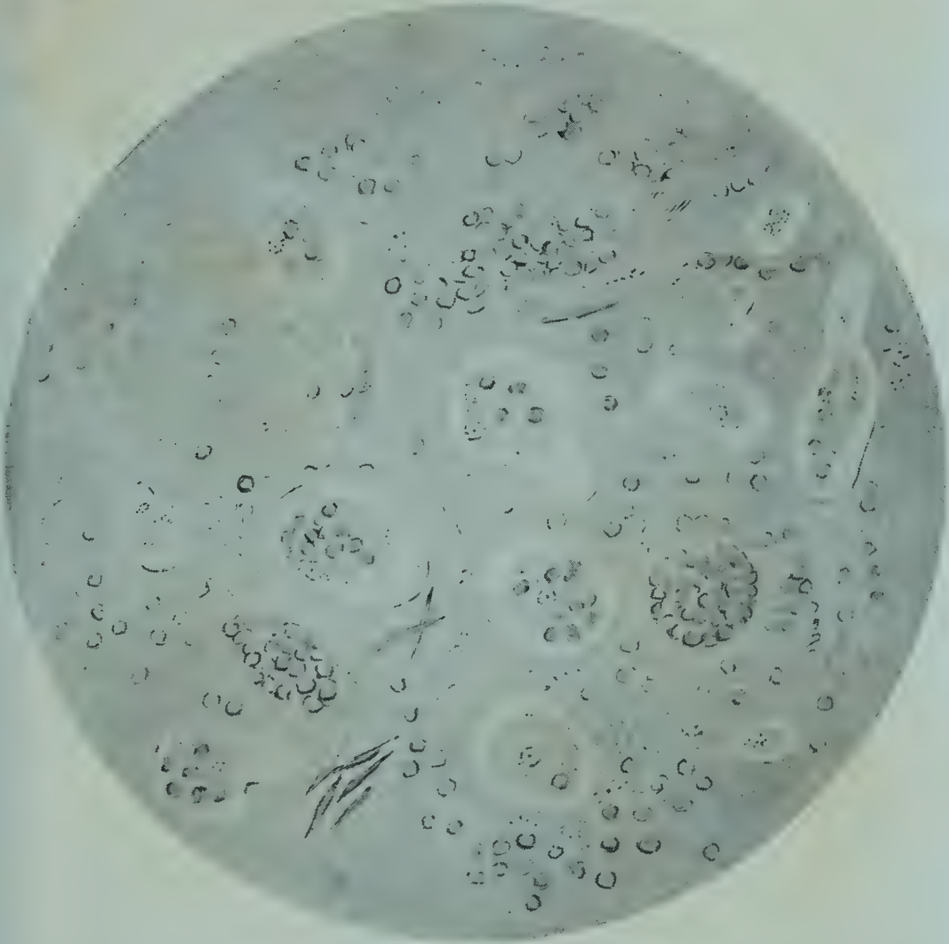

Plate VI. Active *Entamoeba histolytica,* some with ingested blood corpuscles, in the stools of Amoebic Dysentery. Note rouleaux of erythrocytes and charcot-Leyden crystals.

gastric juice, but soluble in trypsin) hatch in intestine of new host into quadrinucleate amœbulæ, which, escaping by a small pore, divide by mitosis, giving rise to eight uninucleated metacystic individuals. These feed on bacteria in the lumen of the bowel and are known as lumen or "*minuta*" forms.

Alternative or coprozoic cycle, described by Hoare in the symptomless or cyst-carrier state. In this the lumen-dwelling amœbæ (*minuta* forms) live on bacteria in the bowel and produce cysts in the fæces.

Non-pathogenic human amœbæ resembling E. histolytica

Entamœba moshkovskii which resembles *E. histolytica* in every detail: discovered in 1941 in sewage in Russia, and confirmed in the U.S.A., England and Brazil, is non-pathogenic to man and laboratory animals.

E. invadens, a common parasite of snakes, is also morphologically identical.

Entamœba coli.—Inhabitant of intestinal canal of over 50 per cent. of normal individuals in tropics, often found in fæces of bacillary dysentery and other intestinal diseases ; normally lives in fæces. Not infrequent in temperate climates. Individuals, on average, larger (10–40 μ), with sluggish movements and gradual extension of pseudopodia. Cytoplasm bulky, granular, contains food vacuoles, bacteria, yeasts, occasionally cysts of other amœbæ and intestinal protozoa. No differentiation between ecto- and endoplasm ; does not ingest r.b.c. *Nucleus* large, coarse, with nuclear ring visible in living state. Cysts larger than those of *E. histolytica* (10–30 μ), variable in size ; number of nuclei varies from 1–8, usually 8. Cytoplasm granular, contains glycogen ; iodine-staining glycogen vacuole with sharp outline disappears before 4-nucleated stage is reached. Chromatoid bodies occasionally rod-like. Cultured on same media as *E. histolytica* ; not affected by emetine.

E. polecki, an intestinal amœba of the Rhesus monkey which resembles *E. coli* very closely, has been reported from man in California.

Endolimax nana, commonly found in fæces in tropics—almost more frequent than *E. coli*—small species (6–12 μ), with granular vacuolated protoplasm containing bacteria or other food material ; nucleus characteristically vesicular. Cysts small, very numerous in fæces, ovoid or spherical (6 μ), usually contain four nuclei, therefore resemble *E. histolytica*. Nuclei characteristic : iodine-staining glycogen, binucleate forms, no chromatoid body, but sometimes long filamentous rods.

Iodamœba bütschlii.—Non-pathogenic parasite of man, monkey and pig, commonly associated with *E. histolytica*. Small amœba in fæces (9–10 μ, sometimes 5 μ) characteristic, vesicular nucleus with well-defined central karyosome. Cysts uninucleated, irregular, spherical or ovoid (6–16 μ). Refractile volutin granules, large dense iodine-staining glycogen mass, cyst nucleus excentric and large. *I. bütschlii* amenable to emetine and emetine bismuthous iodide treatment.

Dientamœba fragilis.—Probably not an amœba, but stage in flagellate allied to *Histomonas maleagridis* (blackhead in turkeys). Small (3·5–12 μ), and actively motile, with marked differentiation between ecto- and endo-plasm. Nucleus has large karyosome composed of granules. Lives on bacteria, does not produce cysts, only survives for short period after passage in stool.

Cultivation of E. histolytica.—From active vegetative forms or from cysts in special media—blood-agar or solidified egg-slope containing starch granules; frequent subculture necessary. Symbiosis with bacteria, usually *Bact. coli*, necessary, but has been grown in tissue culture and in chicken embryo, in absence of bacteria.

Reproduction of disease in animals.—By intrarectal injection of fæcal material, or culture, into cats, dogs, guinea-pigs and monkeys, Cats (kittens) most susceptible.

Cyst carriers (cyst-passers).—In endemic areas *E. histolytica* cysts commonly found in fæces in absence of symptoms; amœbæ ingest bacteria (coprozoic phase); symptomless state may persist or may lead subsequently to intestinal amœbiasis or liver abscess. **Carriers** are healthy individuals without intestinal lesions, but should be treated, as potential source of infection. Carrier rate varies considerably. In England, although indigenous, "amœbic dysentery" as such is almost unknown; carrier rate 2·9–9·7 per cent.; Egypt 11·5 per cent.; parts of Holland, N. Russia and U.S.A., 12 per cent. Rate in Iraq, India, S. China and tropics generally much higher, probably 20–70 per cent.; statistics variable. Carriers discharge up to 6,000,000 cysts per gm. fæces: the total output per day ranging from 330 thousand to 45 million.

N.B.—It is important to remember that ulceration of bowel can exist without symptoms. In New Orleans lesions found in 6 per cent. of routine accident autopsies.

Contact-carriers with healed ulcers: no evidence of infection, but cysts present, produced by *minuta* coprozoic forms.

Convalescent carriers.—On partial recovery from amœbic dysentery with ulcers still active.

PATHOLOGY

In majority of cases infection is limited to lumen of bowel and amœbæ live on surface of mucosa and among bowel contents where they ingest bacteria, starch granules and fæcal debris, so that bacteria can be demonstrated in amœbæ by staining, as in cultural forms. Owing to poor diet in human intestine they remain small (*minuta* forms). Possibly majority of cyst-passer cases harbour this coprozoic, commensal, harmless form. When bowels are normal and formed stools are passed, the cysts in the fæces afford only evidence of amœbic infection, but when stools are loose, medium-sized amœbæ, containing ingested bacteria may be passed. *E. histolytica* inhabiting the gut lumen, and producing cysts, lives in harmony with host as commensal. When some trauma to the mucuous membrane of the bowel is produced, possibly from bacterial infection (Westphal), the host-parasite relationship is altered, as *E. histolytica* is potentially pathogenic and develops virulent properties, manifesting itself by invasion of the intestinal wall. The amœbæ then attach themselves to the mucosa and secrete a cytolysin which destroys the host-cells and invade submucosa. This produces local necrosis, abscess formation and a flask-shaped ulcer. Precystic forms are evolved, then cysts, which pass into fæces and are voided. Small submucous abscesses form ulcers in long axis of large intestine : cæcum, hepatic flexure, rectum, splenic flexure (mostly cæcum and sigmoid) ; lower portion of small bowel involved rarely. Blood vessels show engorgement and thrombosis. Intervening mucosa normal. Healing (granulation tissue) leaves slate-coloured parchment scar. Ulcers vary greatly in size, may extend down rectum to anal margin ; contain black sloughs (Dyak-hair sloughs), or " sea anemone " ulcers. Thickening and hypertrophy of bowel wall are seen. There may be also sacculations and cicatricial contractions. Thrombosis of deep blood vessels (amœbæ in thrombi), gangrene of bowel wall and hæmorrhages. Perforation of ulcers may cause peritonitis or localized pericolic abscess ; amœbic perforation of appendix recorded. Polypoid or gangrenous destruction of mucosa is terminal, due to secondary septic infection. " Amœbic granuloma " or amœboma resembling carcinoma is not uncommon.

Microscopical.—*E. histolytica* in base of ulcers and submucosa produces gelatinous necrosis due to cytolysins, with little surrounding tissue reaction : mostly lymphocytes, mononuclears and plasma cells, and few polymorphs, unless secondary bacterial invasion is present. Portal pyæmia is due to secondary invasion of liver by entamœbæ from thrombosed veins.

Clinical pathology.—In uncomplicated amœbiasis there is no marked anæmia and a moderate leucocyte increase (10–12,000), with low proportion of polymorphs—about 70 per cent.

CLINICAL FEATURES

Incubation period very variable—may be prolonged for years, but in Chicago outbreak 7–77 days. Great majority of cases are chronic with cysts ; acute cases with blood and mucus in fæces rarer. May be diarrhœa only—" amœbic diarrhœa." Generally little interference with general health (" walking dysentery "). Periods of exacerbation alternate with periods of quiescence. Onset is usually insidious ; pyrexia is rare and usually means secondary infection, but " amœbic fever " with high temperature recorded. Abdominal pain and tenderness not so severe as in bacillary dysentery ; usually localized to cæcum and sigmoid, occasionally transverse colon. May simulate all kinds of intestinal disease. Amœbic *typhlitis* with acute cæcal pain may resemble *appendicitis*, differentiation often difficult in absence of *E. histolytica* in fæces. Ba enema may help—distortion of *caput cæci* in amœbic typhlitis: *Appendicitis*, tenderness over McBurney's point, pain on rotation of thigh and usually more pronounced leucocytosis. In hyperplastic form (amœboma) palpable tumours in cæcum and sigmoid resemble carcinoma or tuberculoma, and thickening of sigmoid colon, sometimes, of whole large intestine. Flatulence is common; tenesmus rare. Stools rarely more than 12, usually less; diarrhœa alternating with constipation. Melæna sometimes, but no marked emaciation. Skin often dull, lustreless "myxenoid," with subicteric tinge. Very acute cases with toxæmia are rare. Usually some enlargement of liver.

Atypical cases show constipation, lassitude and fatiguability without obvious signs of disease or marked abdominal manifestations save some discomfort. Latency is a marked feature; may subside with apparent recovery in absence of treatment for 7 years or longer. Solitary indurated amœbic ulceration of rectum of long standing may closely simulate carcinoma.

Amœbic hepatitis, due to acute invasion of liver parenchyma by active *E. histolytica*, may supervene at any time during amœbic infection; seldom, if ever, in primary manifestations, and usually in disease of long standing in acute stage, or in chronic. Pyrexial often, with rigor, hepatic pain, enlarged and extremely tender liver, sweating, and leucocytosis 20–30,000. R. shoulder pain frequent. Responds readily to emetine.

Complications.—Intestinal hæmorrhage, massive gangrene of bowel, perforation, pericolic abscess. Liver abscess most common, rarely abscess of brain, amœbic pericarditis, abscess of spleen, lung, or epididymis; perirectal abscess. Amœbic infection of skin, appendicitis, visceroptosis, sacculation of bowel, occasionally megacolon. May be superimposed on bacillary dysentery or *vice versa*. In Egypt associated with *Schistosoma mansoni*. May be complicated by malaria, black-water fever and kala-azar.

Sequelæ.—Non-amœbic appendicitis, achlorhydric dyspepsia, duodenal ulcer, mucous colitis, occasionally sprue, neurasthenic manifestations.

DIAGNOSIS

Clinical diagnosis may be unreliable (see Table V, p. 102). Chiefly confused with milder forms of bacillary dysentery. Stools offensive, bulky, blood and mucus mixed with fæces resembling "anchovy sauce" or, commonly, much dark blood present. Discovery of *E. histolytica* in fæces—warm stage advisable. *E. histolytica* to be differentiated from *E. coli* and other non-pathogenic amœbæ, from tissue cells, macrophages and histiocytes. *Fæces*: film preparations unstained, search with $\frac{1}{6}$-in. lens, show character of cellular exudate, few polymorph cells, Charcot-Leyden crystals and rouleaux of r.b.c. Staining with Weigert's iodine brings out characteristics of nucleus, especially in pre-cystic and cystic forms. Cysts often scanty, varying in numbers from day to day. Several preparations must be searched over several days in doubtful cases; purging with salines renders *E. histolytica* cysts more numerous in fæces. Concentration and cultural methods may be employed. The formalin-ether concentration for fæcal cysts is the best (Ridley and Hawgood):—1 gm. of fæces is emulsified with 7 c.c. of 10 per cent. formol-saline, and strained through 40 mesh per inch wire gauze into a centrifuge tube. Ether, 3 c.c., is added and mixture shaken vigorously for one minute. It is then centrifuged, accelerating slowly and gradually over a period of two minutes to a speed of 2000 r.p.m. The debris on the surface, together with the whole of the supernatant fluid, is decanted. The upper part of the tube is wiped clear of fatty debris. The deposit is shaken up and poured on to a slide. The concentration achieved is from 20 to 30 times. In cases of doubt, lengthy procedure of wet film fixation and staining with iron hæmatoxylin. Complement fixation reaction (Craig is complicated and of doubtful value. Intradermal test (Scalas) unsatisfactory.

Barium enema sometimes shows filling defects of cæcum and colon, but is merely of suggestive value.

Sigmoidoscopy is useful and should always be employed ; magnifying eyepiece is necessary to detect finer lesions. Mucous membrane of rectum pale, lax, redundant. Amœbic ulcers small with yellow centres, hyperæmic margins and associated submucosal petechiæ ; intervening mucosa normal, occasionally showing granular bleeding patches. In chronic stage small circular pits or depressions (" pigskin pittings "). Amœbic granuloma resembling malignant growths, or chronic indurated solitary ulcers with craggy undermined margins may be seen. Ulcers should be scraped by long-handled Volkmann's spoon and *E. histolytica* demonstrated in large numbers in fresh preparations (saline must not be added)—in 10 per cent. of cases where no amœbæ can be found in stools. Biopsy material may be useful.

Proctoscopy useful as routine, relatively painless, easily performed. Amœbic lesions in rectum visualized and biopsy material thus obtained frequently positive for *E. histolytica* cysts.

Differential diagnosis.—From other forms of dysentery—bacillary and balantidial—from diverticulitis, carcinoma, ulcerative colitis, polypus, polyposis, intestinal tuberculosis and from many other forms of intestinal disease, sometimes also from gastric or duodenal ulcer.

TREATMENT

Emetine is drug of election—sometimes much abused. Does not always eradicate amœbic infection. Routine periodic emetine injections to be deprecated as they tend to render *E. histolytica* emetine-fast.

1. **Emetine hydrochloride,** given by injection (deep subcutaneous or intramuscular—never intravenous) : to adults, gr. 1 daily for 8–12 days. In more prolonged course, toxic effects are produced : myositis, neuritis, rapid fall in blood pressure, auricular fibrillation, fine branny desquamation of skin, atrophy of nails, mental and physical depression. *N.B.*—Emetine injections should not be given to patients leading an active life with physical exertion. *Emetine exerts direct effect on active vegetative E. histolytica, but little on cysts*, therefore especially effective in amœbic hepatitis and early cases of liver abscess. In all cases of amœbic dysentery it must

be supplemented with subsequent course of emetine bismuthous iodide. Owing to apparent failures of emetine treatment during recent war it has been assumed that amœbæ readily become emetine-resistant. This appears to be due to inadequate initial emetine treatment.

2. **Emetine-bismuthous-iodide** (E.B.I.), given as red powder in hard gelatin capsules, or slipules. Enteric-coated tablets (emplets) tend to pass through intestinal canal undissolved ; decompose in large intestine where emetine is set free. Acts as intestinal irritant and emetic. Dose: 1–3 gr.; course of 3 gr. (0·18 gm.) for 10 days is sufficient. Total dosage, 19–36 gr. (1·2–2·16 gm.). Patient must be kept in bed. If given at 10 p.m. no solid food must be taken after 4.30 p.m.; luminal, allonal or tinct. opii should be given at 9.30 p.m. There is usually nausea during night, and diarrhœa. *E. histolytica* cysts disappear on third day. E.B.I. eradicates greater part of infection, but is not always effective in preventing subsequent relapses in long-standing infections, especially after prolonged previous courses of emetine injections. It is best combined with quinoxyl (see below). *Emetine periodide* (E.P.I.) is less irritating than E.B.I., but probably less effective. It is indicated in those intolerant to E.B.I., in the same or larger doses. *Auremetine* also easily tolerated, 1 gr. t.d.s.
3. **Quinoxyl (Chiniofon-Yatren),** oxy-quinoline-sulphonic acid with iodine, is best administered in the form of retention enema in 2½–5* per cent. solution in 7 oz. (207 c.c.) water, to be retained 6–8 hours, daily for 10 days, heals amœbic lesions in rectum. Foot of bed must be raised, and a pillow placed under buttocks. This treatment is not widely used, but is effective in this condition.
4. **Combined treatment** effective, especially in chronic cases. Quinoxyl retention enema daily for 10 days, E.B.I., 3 gr. (0·18 gm.) every night for same period. Light diet before 6 p.m. Dietetic restrictions needed in after-treatment—especially avoidance of starches. Alcohol forbidden for one month. Other forms of combined treatment—emetine, emetine bismuth iodide and diodoquin.
5. **Penicillin injections and sulphonamides.**—Amœbic cases with pyrexia are usually due to secondary infection of amœbic ulcers in intestine. In these cases injections of penicillin, though without action on amœbæ, prove most beneficial. Many believe emetine and E.B.I. therapy is enhanced by injections of penicillin, 1·5 mega units, in addition to 20 gm. sulphasuccidine daily for 5 days.
6. **Antibiotics.**—A number of the newer antibiotics have been tried out in treatment. In almost every case the first results have been favourable. The main forms are aureomycin, terramycin (tetracycline), bacitracin and fumagillin. There is no doubt that they stop the diarrhœa, influence symptoms and vegetative amœbæ and cysts disappear from the stools. Opinions vary as to how these results are obtained. Although it has been shown that

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* 5 per cent. is saturation point.

aureomycin and fumagillin act upon the amœbæ in culture, some believe that the action is indirect, by destruction of their food bacteria in the fæces. Although immediate effects are good, they are not lasting, so that relapses ensue after a remission of a month. It is probable that the most durable effects are produced by the combination of antibiotics with emetine or E.B.I.

Aureomycin (achromycin and erythromycin) by mouth, 0·25 gm. 4 times daily at 6-hour intervals for 15 days, has instantaneous effect upon the symptoms of amœbic dysentery and the ulcers heal rapidly. The disappearance of the amœbæ is rapid and dramatic. By the 4th day the majority are clear of amœbæ.

7. **Other drugs.**—Stovarsol, carbarsone (Eli Lilly), arsenical preparations containing 27 per cent. arsenic, tablets or pulvules, 4 gr. (0·25 gm.), twice daily for 10 days. Milibis (Wia) is a bismuth-arsenical; in tablets of 0·25 gm., three times daily, for seven days, is widely used in the chronic stages. Nivembin is a combination of chloroquine 65 mgm., and di-iodo hydroxy-quinoline 300 mgm. Diodoquin (dihaloquin) contains 63·9 per cent. iodine; somewhat similar in composition to iodochloroxy quinoline (enterovioform). Valuable in the treatment of chronic amœbic dysentery—especially in symptomless cyst carriers. Tablets 3·2 gr. by mouth, 8 daily for 15 days.

Treatment of amœbic hepatitis.—Patient kept strictly in bed. Hot applications (antiphlogistine) over liver. Liquid diet, saline purge. Emetine injections—usually 8 gr. (0·51 gm.) suffices (1 gr. for 8 days). Chloroquine (*aralen*) (see p. 245) 0·25 gm., t.d.s. combined with emetine—concentrated in liver—has specific action on metastatic amœbæ. For persistent pain : dry cupping. Aspiration of liver (hepatic phlebotomy) may prevent development of hepatic abscess. (Occasionally, amœbic hepatitis is prelude to amœbic abscess.)

PROPHYLAXIS

Depends upon efficient sanitation, uncontaminated water-supply, and measures against houseflies in subtropical countries where they are excessively prevalent. Sand-filtered water is free from cysts, but chlorination is quite ineffective. Unboiled water, raw vegetables and fruit, possibly contaminated by human fæces, must be avoided, and food-handlers examined for *E. histolytica* cysts. Coolies, orderlies and others so infected should not be employed ; this is especially important in war time. Cyst carriers should be treated by E.B.I. and diodoquin. Cysts survive in fæces at room temperature 2 weeks: in refrigeration 2 months. High temperatures kill them in a short time. 1 : 2500 solution of bichloride of mercury and 1 per cent. carbolic or lysol kills in 30 minutes. Fæces disinfected by 1 : 200 aqueous solution of cresol for 15 minutes.

Chemoprophylaxis.—Quinoxyl tablets, 4 gr. (0·25 gm.), or diodoquin, taken at night in hyperendemic areas may possibly serve as prophylactic. Further experience necessary.

SECONDARY AMŒBIASIS. COMPLICATIONS OF AMŒBIASIS

HEPATIC ABSCESS (Liver abscess. Hepatic Amœbiasis).

GEOGRAPHICAL DISTRIBUTION

Corresponds with that of amœbic dysentery.

ÆTIOLOGY

Relationship to amœbic dysentery undoubted ; attack of dysentery may antedate onset by 20 years or longer, but always infection with *E. histolytica* cysts, or cryptic ulceration of large intestine, usually cæcum. More common in Europeans than natives ; men specially affected ; women rarely ; children hardly ever, except in Durban. Most common age : 20–40. Right lobe of liver usually affected. *E. histolytica*, active vegetative form, found in liver pus ; cysts never. Rarely associated with amœbic pericarditis.

PATHOLOGY

At first solitary or multiple, gummatous, greyish-yellow areas in centre of liver, which afterwards break down to form reddish, gummy pus in ragged cavity without limiting wall. *E. histolytica* found in numbers at margin of abscess ; in liquefied pus they disappear. At first sterile, it later may become secondarily infected with streptococci or other organisms, *B.* (*Escherichia*) *coli* and *Salmonella enteritidis*. Single abscess may be large and occupy almost whole liver. Multiple, may be five or more, size of filbert, in one lobe, with miliary small abscesses scattered throughout surrounding parenchyma, causing intense hyperæmia. Rupture of liver abscess through valve-like aperture in diaphragm is not uncommon: secondary lung abscess forms in base of right lung; may also rupture into other viscera (see p. 53). Liver pus: characteristic chocolate colour, streaked with mucus, often thick and viscid; may resemble badly-made custard; odourless except when secondarily infected; then often green and offensive. Contains pigmented spherical cells, leucocytes with glycogen granules, oil globules, lecithin plaques, cholesterol crystals, Charcot-Leyden crystals, and occasionally *E. histolytica*. Pus becomes inspissated and absorbed and walls of cavity thick, resistant, fibrous, even cretified. Calcification may prevent collapse and subsequent healing. Encountered often in cases without history of amœbiasis.

Bilaterality of liver.—Portal stream divided anatomically between right and left lobe. Therefore, on destruction of parenchyma of right lobe, hypertrophy of left takes place, often forming palpable tumour in left hypochondrium.

CLINICAL FEATURES

Great variety of symptoms ; subjective may be absent. Generally fullness, weight and stabbing pain in right hypochondrium. Subicteric look ; furred tongue ; pyrexia, night sweats, loss of weight ; rheumatic pains at night. Right shoulder pain in considerable proportion—reflex irritation of phrenic nerve through doming and stretching of diaphragm. Pain referred to left shoulder from abscess in left lobe. Pyrexia: progressive, hectic, most marked at night. Often fullness and bulging of epigastrium or mid-axilla. Liver tender, enlarged—usually downwards. Hepatic pain relieved by lying on affected side. Dullness at base of right lung may be due to compression-pneumonia by enlarged liver or secondary involvement of lung and pleura. Often pleural effusion (ægophony) and pleuritic rub. Amœbæ and pus cells present in effusion. Blood: rarely no change; usually leucocytosis 15–35,000 (polymorphs rarely above 80 per cent.), and severe secondary anæmia, rarely of pernicious type. Death from toxæmia, cholæmia, rupture of abscess; septicæmia.

Varieties.—May be acute: complete destruction of liver tissue and rapid death, or chronic: palpable obvious tumour in epigastrium, mid-axilla, or base of scapula; spontaneous rupture. Marked rigors rare. Enlarged cervical, axillary and supraclavicular glands not uncommon. Dysphagia: pain on swallowing when bolus traverses lower end of œsophagus. Localized pain on pressure in intercostal spaces is valuable sign. Cough, due to reflex irritation of diaphragm. Local œdema of chest wall and bulging may indicate site of abscess. Jaundice uncommon; may be due to toxæmia from secondarily-infected abscess, or from obstruction of biliary ducts.

Rupture into bronchus: hæmoptysis and severe cough, prune-juice sputum; often clubbed fingers; likely, in chronic cases, to be mistaken for tuberculosis. Melæna may occur. Rupture into pleura (with pneumothorax), pericardium, peritoneum, stomach, colon, through skin of abdominal wall or axilla (amœbiasis of skin may result) or into common bile duct (bilious fistula).

Mortality.—Formerly high, 50 per cent.; due in part probably to operative measures then in use. Now minimal with better diagnosis and treatment by aspiration combined with emetine injections and chloroquine (*aralen*).

DIAGNOSIS

Not always easy.

Common mistakes: (1) Failure to diagnose hepatic disease; (2) mis-interpretation of basal pneumonia as secondary to intrahepatic suppuration; (3) attributing pyrexia to some other fever (malaria); (4) mis-diagnosis of other intrahepatic disease as liver abscess—*e.g.*, suppurating hydatid, gumma, pylephlebitis, gall-stones, cholecystitis, subphrenic abscess, appendix abscess, localized abscess of abdominal or thoracic wall; abscess of liver associated with diverticulitis, duodenal ulcer and, rarely, with ascaris infection, melioidosis; pleurisy, encysted empyema, pyelitis, schistosomiasis (*S. mansoni* and *S. japonicum*), ulcerative endocarditis, kala-azar, malignant disease of the liver, non-parasitic cyst. Differential diagnosis from suppurative cholecystitis, in absence of X-ray examination, particularly difficult.

Diagnostic Rules.

(1) Suspect liver abscess in all cases of progressive ill-health associated with abdominal signs and pyrexia, particularly if accompanied by sweats, pyrexia and leucocytosis.

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(2) Low-grade pneumonia at base of right lung suggests intrahepatic suppuration.

(3) Fæces examination : *E. histolytica* cysts found in 45–50 per cent. by concentration methods.

(4) X-ray examination and screening of excursions of diaphragm shows limitation or fixation of movement, paradoxical movement, doming, tenting, or " peaking " and sometimes alteration of cardio-phrenic angle to right angle. Abscess in centre of liver may be visible, especially when margins are cretified. Fluid level can be visualized by injection of air or lipiodol.

(5) Blood examination : leucocytosis usual.

(6) Diagnostic aspiration : needle inserted at point where abscess lies closest to surface, performs up and down pendulum movements with respirations on entering cavity. Withdrawal of pus and examination.

TREATMENT

(1) **Method of election.**—Emetine injections in pre-suppurative stages up to 12 gr. (0·76 gm.) produce reduction in size of liver, abolition of fever and pain. Chloroquine (0·25 gm. t.d.s. for 7 days, thereafter 0·25 gm. b.d. for 10 days: maintenance dose 0·25 gm. daily), is concentrated in liver appears to be specific for hepatic amœbiasis. Nivaquine (chloroquine sulphate) equally effective. Antibiotics—aureomycin and terramycin (oxytetra-cycline) much used, but not permanently effective unless combined with emetine. Afford protection against secondary infection.

After-treatment with E.B.I. to clear out intestinal infection and to prevent recurrence (combined treatment, p. 48).

(2) **Aspiration.**—If much pus has formed, aspirate with Potain's aspirator, draw off 20 oz. (591 c.c.) or more ; pus may re-accumulate ; repeat aspiration, and continue with emetine treatment and chloroquine. If pus is too viscid, inject eusol (equal parts with saline) into abscess cavity. If secondarily infected with bacteria inject penicillin—mega unit—into abscess cavity.

Rules.—Never aspirate with Potain's aspirator unless all preparations are made for open operation and electric sucker is at hand. Gas and oxygen anæsthesia. The spot to be selected is indicated by physical signs ; preferably between 8th and 9th intercostal spaces, well below line of pleura, in anterior axillary line, 1½ in. along costal margin. Insert needle upwards, inwards, backwards, for not more than 3¾ in. (distance of *inferior vena cava* from any part of chest wall is 4 in.). Needle swings when liver is entered ; push it gently forwards until sense of resistance shows that it is in abscess cavity ; affix syringe and aspirate. If costo-phrenic sinus is crossed and there are adhesions, pus is indicated.

Indications for open operation.

(1) When, after repeated aspirations, no pus is obtained, but indications of its presence are too strong to be ignored. (May be multiple small abscesses.)
(2) When abscess points in epigastrium, indicating left lobe abscess. Care must be taken to avoid colon and duodenum.
(3) Where large amount of pus is present, is secondarily infected and has not yielded to aspiration.

Technique of open operation.

Abdominal route.—Kocher's subcostal incision. Pack off wound edges. Insert wide bore sucker straight into liver to prevent extravasation. Insert finger into cavity, break down loculi. Suck out all pus. Stitch edge of cavity to parietal peritoneum. Insert wide drainage tube (Tudor Edward's empyema tube drain); push to bottom of cavity.

Transpleural route.—Clear and resect 1½ in. of 8th and 9th ribs in posterior axillary line. Stitch diaphragm to thoracic wall; may be difficult on account of fragmentation of diaphragm.

Simpler method.—Expose ribs, denude of tissues, insert iodine gauze pack beneath ribs, leave 3–4 days. Adhesions form in costophrenic sinus. Ribs resected and infection of pleural cavity prevented. Insert sinus forceps and use aspirator. Insert wide-bore tube to ensure free drainage. No shortening of tube, but let cavity extrude it automatically, maintaining it *in situ* as long as there is free drainage. Irrigate with Dakin's solution, which has solvent action on wall of liver abscess.

Prognosis good in most cases. If condition is cured and underlying amœbic infection eliminated, there is no bar to return to tropics.

Treatment of abscess rupturing into lung.—When emetine does not influence fever or diminish symptoms and signs, then operative measures must be undertaken, especially if amount of expectorated pus increases and patient loses weight. Ribs are resected, lung explored and drained, as for abscess. May also be necessary to explore liver, but abscess cavity may be collapsed with opposed walls. Aspiration preferable to open operation.

Rupture into pleura: operation as for empyema; into peritoneum, then laparotomy and drainage. Into pericardium: open and drain if possible, but aspiration, repeated, may suffice.

PULMONARY AMŒBIASIS

Solitary or multiple amœbic abscesses of lung. Solitary abscess, if not amenable to emetine treatment, must be operated as for lung abscess. If multiple, response to emetine is usually striking. Marked pyrexia, signs of bronchopneumonic consolidation, marked leucocytosis. X-ray may assist diagnosis.

AMŒBIC ABSCESS OF BRAIN

Excessively rare; may respond to emetine, but generally fatal; usually secondary to hepatic abscess.

AMŒBIC ABSCESS OF SPLEEN, PERICARDIUM, EPIDIDYMIS AND VAGINA

Splenic abscess excessively rare, associated with hepatic abscess. Amœbic pericarditis may be primary, but usually secondary to hepatic abscess. Treated on surgical lines. Rarely, genito-urinary amœbiasis may be associated with presence of *E. histolytica* in the urine. Amœbic ulceration of vagina reported from India.

AMŒBIC INFECTION OF SKIN

May be secondary to ruptured liver abscess and associated with rib necrosis, or of abdominal wall secondary to operations on bowel, such as colostomy or opening of perirectal abscess. Massive gangrene of abdominal parieties : much dark, evil-smelling, anchovy-sauce pus containing active amœbæ. Response to emetine injections remarkably effective and rapid. Perirectal abscess may rupture and spread to skin of buttocks and back, causing great tissue destruction. May occur in patients with *E. histolytica* cysts in fæces, in absence of dysenteric symptoms.

BALANTIDIASIS

Infection of large intestine with ciliate protozoan, *Balantidium coli*, producing symptoms and pathology resembling amœbic dysentery.

Geographical Distribution.—*Balantidium* is normally a parasite of pigs, and causes fatal disease in chimpanzees in captivity. In man, found in Russia, Scandinavia, Siberia, Georgia, Finland, Germany, Austria, Holland, China, Andaman and Sandwich Islands, Egypt, Sudan, N. America, Brazil, Porto Rico, and England.

Ætiology.—*Bal. coli* is a large, oval, ciliated protozoan (30–200 μ by 40–60 μ), clothed with cilia, with a kidney-shaped macronucleus and approximated micronucleus, food vacuoles, anterior *peristome* and posterior *cytophage* (anus), showing nutrition ingestion of particles. Reproduction is asexual by transverse fission, but conjugation takes place. Cysts are ovoid (50–70 μ) with no cilia, passed in fæces. It is cultured on the same media as *E. histolytica*, frequent subinoculations being necessary.

Pathology.—Resembles amœbic dysentery closely ; parasite found in submucosa, muscular coats, blood vessels, lymphatics and in mesenteric glands.

Clinical Features.—Symptoms closely resemble those of amœbic dysentery, usually chronic and diarrhœic. No specific blood changes.

Diagnosis.—By fæces examination—balantidia scanty, but may be in clumps.

Treatment.—None satisfactory. Carbon tetrachloride 1 dr. (3·69 c.c.), recommended ; also *carobinase*, watery extract of *Jacaranda decurrens*, 25 gm. (365 gr.), in 500 c.c. of hot water, with daily rectal lavage for 3 weeks. *Acranil*, hydrochlorate of acridine recommended in Germany; intramuscular injections of gr. $\frac{1}{8}$ biniodide of mercury said to be specific. *In vitro* 1 : 100,000 solution kills balantidia instantaneously.

GIARDIASIS

Infection of small intestine and duodenum with *Giardia* (*Lamblia*) *intestinalis*.

Geographical Distribution.—World-wide ; extremely common in tropics. In temperate zones, especially in children.

Ætiology.—*Giardia intestinalis:* shape of half pear split longitudinally —12–18 μ by 6 μ. On ventral surface is concave sucking disc and tail terminates in two flagella. Four pairs of anterior flagella arise from blepharoplasts ; two axostyles, with two oval nuclei. Multiplies by binary fission. Cysts in large numbers, bi- and quadri-nucleate (14 μ). Cytoplasm transparent ; axostyles and other structures seen. Stains well with iodine. Cannot be cultured on media.

Pathology.—Pathogenicity doubted by some. Generally considered irritant ; parasite attaches itself by sucking disc to villi and invades biliary tract. Also found in duodenal and gastric juices ; ulceration of small intestine described.

Clinical Features.—May be none. In children especially, and under war conditions, recurrent diarrhœa, abdominal discomfort. Fæces fluid and mucoid, may be greenish or light-coloured, sometimes resembling sprue. Cholecystitis (doubtful) and steatorrhœa described. Flatulence +. Relapses frequent ; quiescent periods ; tolerance acquired. Fæces may contain cysts in enormous numbers.

Treatment.—Difficulty in claiming permanent cure on account of latency. Atebrin (Mepacrine hydrochloride) specific for active stage and for cysts. Dosage 1½ gr. (0·1 gm.) t.d.s. for 7 days. Now abundantly confirmed. Restrict carbohydrates. Mainly protein diet. *Acranil* recommended by German and Scandinavian authorities in doses from 0·25 gm. daily for children under two to 1·5 gm. daily for 5 days in those over ten. Synthetic anti-malarial drugs—chloroquine, camoquin (amodiaquin) and azacrin —are also useful in clearing out cysts.

FLAGELLATE DIARRHŒA

Designation not strictly correct ; presence of flagellates in large numbers probably due to liquid intestinal contents. Small flagellates are extremely common in post-dysenteric diarrhœas and also in dysenteric stools. Though probably non-pathogenic to man, allied species cause intestinal ulceration in laboratory animals, notably guinea-pigs.

Trichomonas hominis: pear-shaped body (10–15 μ by 7 μ), spherical nucleus at anterior end, three long flagella directed forwards, and a thicker fourth backwards, forms border of undulating membrane and free flagellum ; small anterior aperture (cytostome), central skeletal rod (axostyle) ; vacuolated cytoplasm containing food granules. No cysts.

Chilomastix mesnili resembles above in shape and size, occurs in large intestine. Has three long anterior flagella, no undulating membrane or axostyle, large anterior cytostome occupying two-thirds of body and containing flagellum, anterior spherical nucleus, vacuolated cytoplasm with food granules. *Cysts:* lemon-shaped (7–10 μ), rather resemble yeasts.

Treatment.—Intestinal lavage with 2 per cent. sodi. bicarb. Stovarsol or carbarsone, 4 gr., twice daily by mouth for 8 days.

INTESTINAL COCCIDIOSIS

Mild form of mucoid diarrhœa with Charcot-Leyden crystals and cysts of Coccidium—*Isospora belli* (*hominis*)—found occasionally all over world, especially Near East and Dutch East Indies.

Isospora belli.—Not seriously pathogenic. Schizogonic cycle in cells of intestinal wall unknown. Cysts (oöcysts): elongated, oval, with tapering extremity (18–33 μ by 12–16 μ); clear, colourless wall. Oöcysts discharged with zygotes unsegmented, but occasionally with ovoid sporoblasts.

Isospora natalensis from Durban resembles *I. rivolta.* Oöcysts measure 30 by 24 μ. The sporocysts are in the æquatioral position and measure 17 by 12 μ.

CHAPTER II

SPIROCHÆTAL DISEASES

(R.F. = Relapsing Fever; O. = Ornithodorus; P. = Pediculus; Sp. = Spirochæte)

RELAPSING FEVERS

Spirillum fever, tick fever, etc.: a group of closely allied fevers caused by spirochætes and transmitted, either by the louse or by various species of tick (*Ornithodorus*). A number of varieties are now recognized, the clinical characteristics of which are on the whole similar, but vary in intensity in the different geographical regions where the arthropod vectors occur.

GEOGRAPHICAL DISTRIBUTION

Louse-borne type is widely spread in Europe, N. America, N. Africa, Abyssinia and China, rarer in tropical Africa and Malaya. Tick fever (*Sp. duttoni*) is confined to Central Africa, Congo, E. Africa, Uganda, S. Abyssinia and Madagascar, Transvaal and in Graeff-Reinet, Cape Province. Another form of tick-conveyed fever is found in Palestine, Persia and India; special varieties in S. Spain and Morocco, Central and S. America, and California.

EPIDEMIOLOGY

R.F. in Europe in winter; insanitary conditions favour louse. Specially prevalent in war. "Famine Fever," Serbia, 1915, and Russia. Great epidemic (1921); in N. Equatorial Africa, Gold Coast, Senegal, Nigeria, W. Sudan, with high death rate, intense jaundice. In India is a disease of cold weather. Tick fever has no seasonal incidence.

ÆTIOLOGY

The type spirochæte is *Sp. recurrentis* and varieties are morphologically, though not serologically, identical.

The spirochæte is a spiral filament (8–15 μ by 0·2 μ) with pointed ends, each turn having an amplitude of 2–3 μ, with 3, 4 or even 6 bends. In fresh blood exhibits active movements. Larger forms are due to end-to-end attachment of individuals. Great variation in morphology. Spirochætes, in blood during febrile stage, in some cases in very large numbers, disappear before crisis and are scanty or absent in afebrile interval. Demonstrated in thick film by staining methods or dark ground illumination. By electron-microscopy long filamentous flagella can be demonstrated.

Cultivation of *Sp. recurrentis* is best effected by inoculating infected blood beneath chorio-allantoic membrane of chick embryo. The spirochætes multiply in the blood of the embryo and attain maximum development on the fifth day.

TABLE I

VARIOUS FORMS OF RELAPSING FEVER

	Geographical Distribution.	**Course in Man.**	**Insect Transmitter.**	**Serum Reactions.**
1. *Sp. recurrentis.*	Europe, India, China, N. and S. America, N. and W. Africa.	2–4 relapses, duration of attack 5–6, apyrexia 7–10, days.	Louse (*P. humanus*).	Immune serum; not aggltn. *Sp. duttoni.*
2. *Sp. duttoni.*	Central and E. Africa and S. Abyssinia.	Severe; 5–11 relapses. Duration of attack 3, apyrexia 1–8, days. Complications severe.	Ticks (*Ornithodorus moubata.* Also *O. erraticus* and *O. savignyi*).	Immune serum not aggltn. *Sp. recurrentis.*
3. *Sp. sogdianum* (*S. persica*).	Turkestan, Persia, Palestine.	Fairly severe; relapses 1–14, attacks short: average 2–6 days.	Ticks (*O. papillipes*).	No cross immunity with other strains.
4. *Sp. hispanica.*	S. Spain and Morocco.	Fairly severe; relapses 4–6, attacks 3–4, days.	Ticks (*O. marocanus*, *O. erraticus*).	Immune serum; not aggltn. *Sp. recurrentis.*
5. *Sp. turicatæ.*	California, Idaho, Colorado, Texas.	Resembles No. 1.	Ticks (*O. hermsi* (Cal.)) (*O. turicatæ* (Texas)).	—
6. *Sp. venezuelensis.*	Central and S. America (Colombia and Venezuela).	Many cases benign. Others resemble No. 2.	Ticks (*O. venezuelense*, *O. turicatæ*, *O. talaje*).	Immune serum; not aggltn. *Sp. duttoni.*

Reservoir hosts.—Rats, mice, monkeys, chimpanzees, desert foxes, jackals. N. African hedgehogs susceptible. In S. America: monkeys, marmosets and opossum. Suggested that *S. normandi*, a common parasite of rats, mice and shrews in N. Africa, is identical with human spirochætes.

Transmission.—Louse (*Pediculus*) : imbibes 1 mgm. blood containing spirochætes which live a day in its midgut (28° C. or 82° F.), affixed to epithelial cells, some outside ; then disappear for 8 days. Possibility of invisible granular stage. On 8th day reappear in blood of louse, increase rapidly (metacyclic forms) and are found in all parts. Louse becomes bag of spirochætes which persist throughout its life. Never in salivary glands. Re-inoculated into man by scratching, rupturing body, and admitting spirochætes through skin. Experiments demonstrate that man may be *bitten* by infected lice with impunity. Transmission through louse not hereditary. Infection is not injurious to louse. Does not develop in crab louse (*Phthirus*).

Louse (*P. humanus*).—Small flattened insect with mouth parts adapted for sucking, indistinctly segmented thorax and 6–9 segments. Metamorphosis incomplete. Male has spine-like penis. Eggs (nits) adhere to hairs ; young lice are small editions of adult.

P. humanus corporis, *P. h. capitis*, biological varieties of same species. —At 32° C. (89·6 F.) eggs hatch in 8 days, taking up to 5 weeks at lower temperatures. Larva moults three times. Adult female lays 8–12 eggs daily, lives 4–6 weeks. Clothing may be disinfected by storage at 75° F. (24° C.); safe period, 28 days. (For disinfestation methods, see p. 76.) In Central Africa lice also appear to harbour *Sp. duttoni*.

Transmission in tick (*Ornithodorus*).—Differs from that through louse. Spirochætes enter solid organs of tick of both sexes. Found in ovaries of female and in a proportion of eggs—transovarian transmission. In this case spirochætes from tick are present in saliva, excrement and fluid from coxal glands (at aperture at base of front legs). They are not transmitted by biting by *O. moubata*, but towards end of feeding tick evacuates contents of hind gut consisting partly of fæces and partly waste products from Malpighian tubules. Some evidence of exceptions: *O. papillipes* in Palestine transmits by bite only (Adler). In epidemiology of R.F. in C. Africa, localization of infection is characteristic: a community of ticks inhabits particular building or courtyard and people who spend night there become infected. *Sp. duttoni* can be transmitted through the louse, retains its immunologic properties as well as its infectivity for *O. moubata*.

Soft ticks (*O. moubata—Argasidæ*), widely distributed in Africa; Somaliland to Cape and from Congo southwards in West. Rotund or oval, greenish-brown ; leathery integument with granules, marked by grooves. Female larger (8 mm.). In habits resembles bed-bug, lives in huts, cracks, thatched roofs, and makes nocturnal attacks on man and animals when asleep. Eggs, in batches 50–100, hatch in 20 days. Emerges as octopod nymph and goes through several stages. Can survive a long time after one meal of blood : one individual lives several years. Common on camping grounds and routes of travel, in mats, bedding, porters' loads. Avoids light, *e.g.*, night-lights. Stupefied by pyrethrum powder. DDT also effective. Water-dispersible powder "P 530" containing 6 per cent. *gammexane* (666, or benzene hexachloride) is lethal to *Ornithodorus*, *Argas* and indeed to all forms of ticks.

In some parts of Africa and S. Abyssinia is replaced by *O. savignyi*, which differs in having minutely-pitted dorsal surface, diurnal habits, and eyes ; frequents market places, cattlestands, etc. Generally considered to transmit R.F. ; opinions differ. Other species of O. roughly resemble *O. moubata*.

TABLE II

	Epidemic Louse. R.F.	**African Tick Fever.**	**Other Tick Fevers.**
Vector	*P. humanus*	*O. moubata*	Other species of *O.*
Haunts	Human body and clothes.	Floors, cracks, courtyards.	Rodent burrows, Piggeries.
Transmission	Crushed louse ; not hereditary.	Coxal fluid, fæces; hereditary.	In some cases doubtful; hereditary.
Reservoirs	Man.	Probably man only. May be mice or shrews.	Rodents, squirrels, and a few other animals.
Biology	Only in man; short-lived.	Feeds mainly on man; lives months or years.	Feeds on animals, occasionally man ; lives months or years.
Disease Type	Epidemic.	House disease.	Sporadic.
Control	Louse control.	Destruction of building ; concrete. Kerosene emulsion.	Difficult ; based on habits of normal hosts or ticks.

Other methods of transmission.—Spirochætes may penetrate mucous membranes and abrasions of skin. Nurses and doctors infected from blood, blood transfusions, etc. Transplacental transmission has been recorded; in one instance in triplets. The fever commences 10 days after birth.

PATHOLOGY

Spleen : enlarged, softened, multiple infarcts, may rupture. Liver, kidneys, heart : cloudy swelling, toxic damage. Sections of spleen and liver show spirochætes within endothelial cells and phagocytes, in former in miliary necrotic lesions in Malpighian bodies. Skin icteric, usually petechial. Bone-marrow : hyperæmic with increase of leucoblastic elements, and phagocytosed spirochætes.

Immunity.—Immune bodies in serum + at crisis ; spirochætes clumped, broken up into granulations. *Sp.* of initial attack differ serologically from those of first relapse : alternation of serological strain, antibodies temporary in blood, also proved by adhesion phenomenon (Rieckenberg test).

PLATE VII

HUMAN INTESTINAL PROTOZOA

(Mostly iodine-stained preparations)

Entamœba histolytica.

1.—Active vegetative form as seen in fresh fæces.

2.—Precystic form.

3.—Uninucleated cyst.

4.—Quadrinucleated cyst with glycogen masses and chromidial bars.

5.—Quadrinucleated cyst—small race.

Entamœba coli.

6.—Active vegetative form in fresh fæces.

7.—Precystic form.

8.—Binucleated cyst.

9.—Octonucleated cyst with chromidial bars.

Endolimax nana.

10.—Active vegetative form in fresh fæces.

11.—Precystic form.

12.—Uninucleated cyst.

13.—Quadrinucleated cyst.

Iodamœba bütschlii.

14.—Active vegetative form in fæces.

15.—Mature cyst with one nucleus and iodine-staining vacuole.

Giardia intestinalis.

16.—Active form in fæces.

17.—Binucleated cyst.

18.—Quadrinucleated cyst (end-on view).

Chilomastix mesnili.

19.—Active form in fæces.

20.—Mature cyst.

Trichomonas hominis.

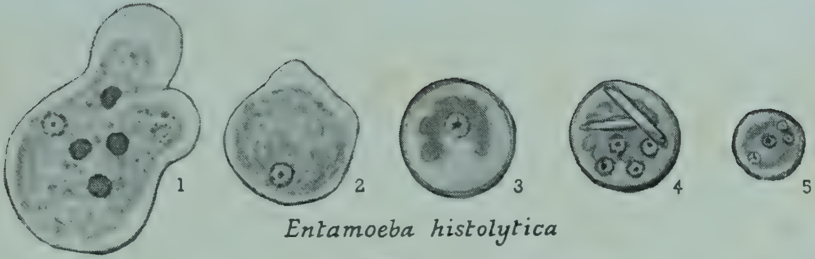
21.—Active form in fæces (no cysts known).

Blastocystis hominis (yeast-like organism).

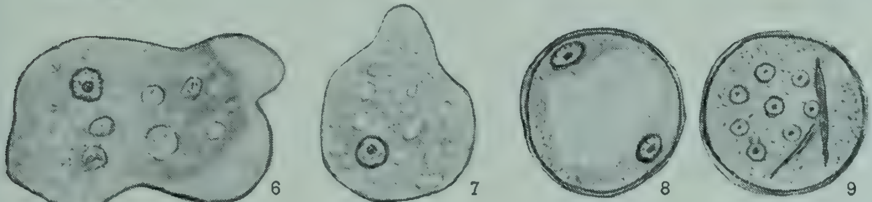
22.—Various forms in fæces.

Balantidium coli.

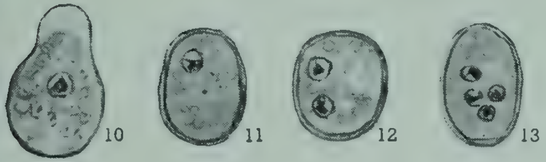
23.—Active form in fæces.



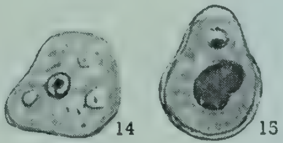
Entamoeba histolytica



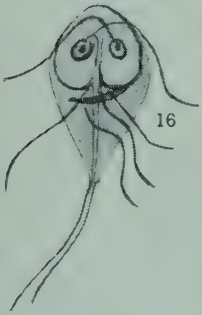
Entamoeba coli

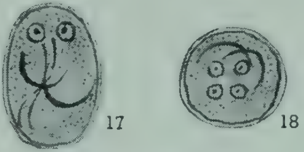


Endolimax nana

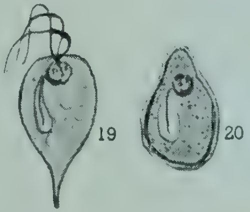


Iodamoeba bütschlii

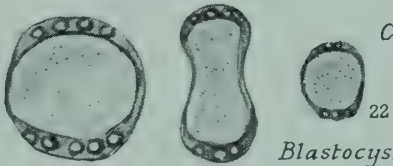




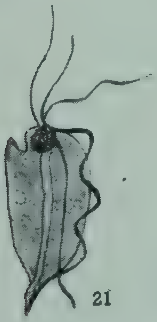
Giardia intestinalis



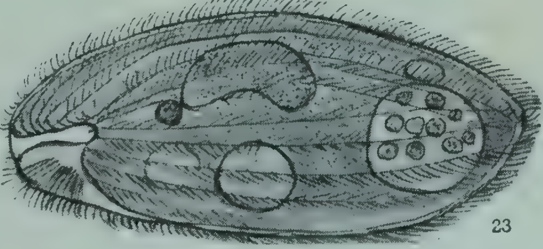
Chilomastix mesnili



Blastocystis hominis

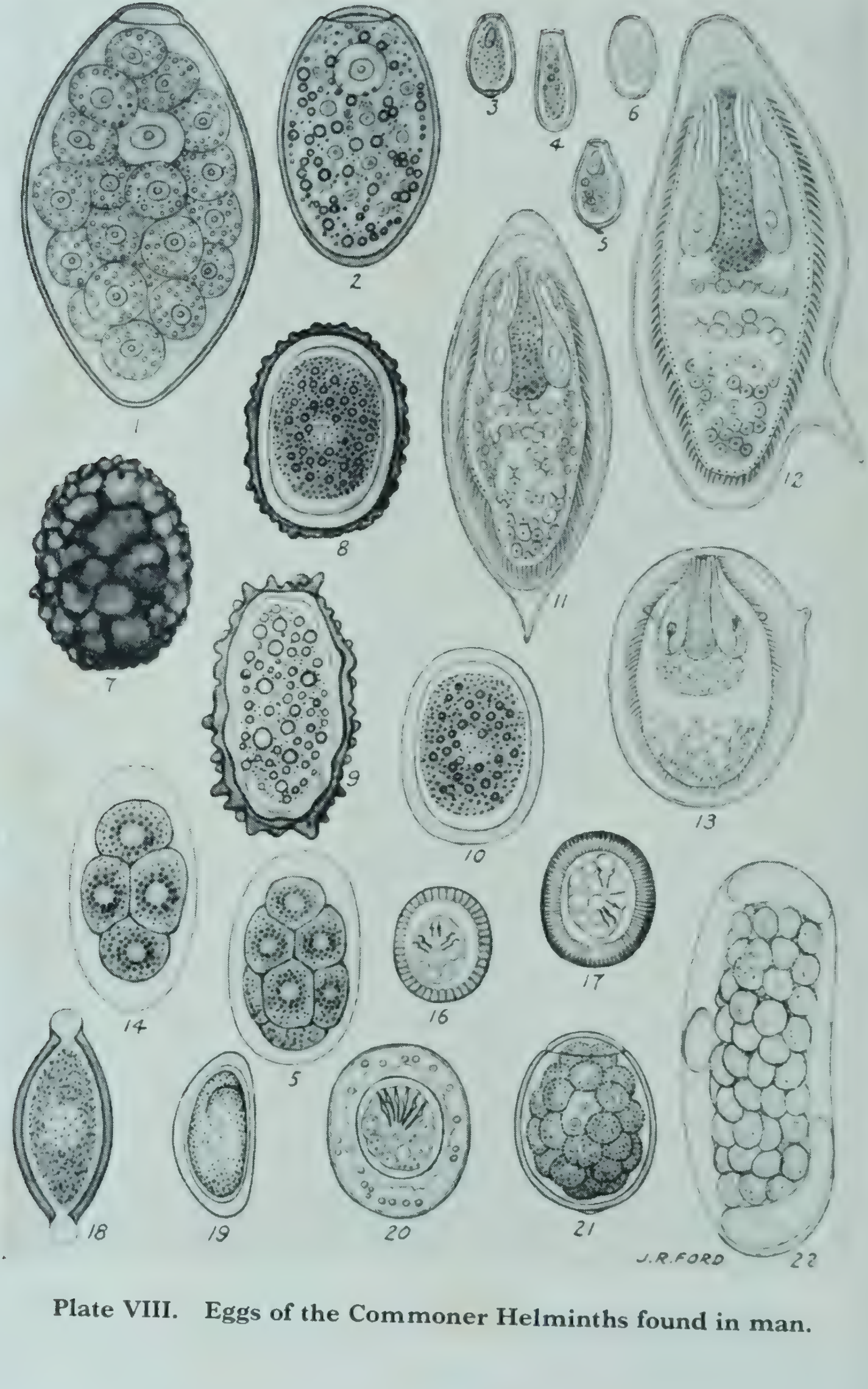


Trichomonas hominis



Balantidium coli

Plate VII. Human Intestinal Protozoa.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J.R.FORD

Plate VIII. Eggs of the Commoner Helminths found in man.

PLATE VIII

EGGS OF THE COMMONER HELMINTHS FOUND IN MAN. × 400

1.—*Fasciolopsis buski.*
2.—*Paragonimus ringeri.*
3.—*Heterophyes heterophyes.*
4.—*Opisthorchis felineus.*
5.—*Clonorchis sinensis.*
6.—*Metagonimus yokogawai* (Yokogawa's fluke).
7.— *Ascaris lumbricoides* (external aspect).
8.— „ „
9.— „ „ (unfertilized egg).
10.— „ „ (decorticated egg).
11.—*Schistosoma hæmatobium.*
12.— „ *mansoni.*
13.— „ *japonicum.*
14.—*Ancylostoma duodenale.*
15.—*Trichostrongylus colubriformis.*
16.—*Tænia solium.*
17.— „ *saginata.*
18.—*Trichuris trichiura.*
19.—*Enterobius vermicularis.*
20.—*Hymenolepis nana.*
21.—*Diphyllobothrium latum.*
22.—*Heterodera radicicola* (non-parasitic, ingested with root vegetables).

CLINICAL FEATURES

1. USUAL TYPE.—Louse-borne form (*Sp. recurrentis*).

Course and severity : vary greatly in single outbreak. Incubation period : 2–10 days. Often complicates typhus.

Onset : sudden, rigor, epistaxis, vomiting, photophobia, headache +. T., 104° F. (may be higher) ; pulse, 110–130. Delirium. Skin : dry, burning, icteric tint. Spleen : enlarged, tender. Tongue : dry, furred. Abdominal pain ; muscular pains in legs. *Herpes labialis.* Occasionally, erythematous rash, rose-coloured macules or petechiæ, in lateral distribution on neck, shoulders, chest and abdomen.

Primary remittent fever 5–7 days, evening temperature highest ; increased pyrexia on 4th, 5th or 6th day, with delirium. Crisis : profuse diaphoresis and diarrhœa ; sudden drop of temperature to subnormal ; collapse ; shrinkage of spleen.

Initial fever = first *paroxysm,* followed by first apyrexia, first relapse, second apyrexia and so on. Relapses may be more severe, but as disease progresses, become milder. Usually five, but number varies in different types. Polyuria before crisis. then diminution of urine. Leucocytosis 15–13,000. Polymorphs 80 per cent. or over, especially during pyrexia. Bilirubinæmia in pre-critical period: indirect Van den Bergh reaction +.

Anomalous types.—In Abyssinia (1940) : dyspnœa, hepatitis and diarrhœa. Pyrexia may be frankly intermittent, with longer periods of apyrexia (17–42 days). Arthritis may supervene. Convalescence protracted, with nephritis, conjunctivitis, iritis, otorrhœa, polyarthritis, pneumonia, neuritis, parotitis, adenitis, and abortion. Abdominal pain may resemble appendicitis.

Severe type.—Bilious typhoid of Griesinger with hæmatemesis, intense icterus, splenomegaly, purpuric hæmorrhages and albuminuria ; apt to be mistaken for yellow fever (*q.v.*), as in Senegal in 1921. Stupor, tympanites and hiccough. Usually seen in war time.

2. CENTRAL AFRICAN TYPE (Carapata disease ; tick fever).—*Sp. duttoni*, more severe, as a rule. Initial fever usually shorter—3 days. Diarrhœa and gastro-intestinal disturbances common. Apyrexial periods irregular. Five or six relapses the rule ; may be eleven. Fever, though shorter, is as severe in relapses as in initial paroxysm. Rarely, fever takes low chronic form with severe headache and vomiting. Iritis is common complication as well as sequela. Liver and spleen enlarged. Bronchitis and pneumonia frequent. Parasites in peripheral blood usually scanty. Polymorphonuclear leucocytosis and usually a moderate aplastic anæmia.

Fulminating cases observed in European soldiers in E. Africa : spirochætes in large numbers ; death in 24 hours, with toxæmia and intense icterus, due to impaction of masses of spirochætes in liver and cerebral capillaries. In natives much less severe, due to partial immunity.

Neurotropic.—Characteristic feature of *Sp. duttoni* infection is neurotropic tendency due to invasion of C.N.S. In recent work in Tanganyika no spirochætes were found in C.S.F. but injection of it into mice produced infection. Signs of meningitis observed; C.S.F. under pressure and contains excess of lymphocytes. Optic atrophy is a serious feature and may accompany the fever or follow after lapse of months. Aphasia seen and also destruction of nuclei of cranial nerves: 3rd, 4th, 5th (ptosis, strabismus, trigeminal neuralgia), 7th (facial paralysis), 8th (deafness).

3. PERSIAN TYPE (mianeh disease).—*Sp. sogdianum* or *persica.* Syria, N. Palestine, Persia; intermediate between 1 and 2; relapses numerous and short; spirochætes in blood scanty. Temperature may come down by lysis. Relapses may last 1–3 days. Occasionally severe, with jaundice.
4. SPANISH TYPE (*Sp. hispanica*).—Incubation period: 1–2 days. Nausea, headache, congestion of face and eyes; herpes labialis common. Periods of apyrexia and relapse correspond to 2; usually four relapses. Lymphadenitis and nerve complications noted.
5. CENTRAL, S. AMERICAN AND CALIFORNIAN TYPES.—More or less resemble 2. Mortality usually below 6 per cent. More severe in aged and young, or when complicated by other disease, as typhus.

DIAGNOSIS

On character of fever, leucocytosis, splenomegaly, icterus, and presence of spirochætes in blood in pre-critical period. W.R. and Kahn positive in pyrexial and apyrexial period in 20 per cent. (pseudo-positive reaction).

Differential diagnosis.—From leptospirosis (Weil's disease), typhoid, typhus, influenza, dengue and in W. Africa from yellow fever. Infarction of the spleen simulates an acute abdomen.

TREATMENT

Nursing and dieting important, especially after crisis.

Salvarsan and neosalvarsan (0·3–0·9 gm.; 4·6–13·8 gr.) intravenously destroy spirochætes and provoke artificial crisis. Novarsenobillon and neosalvarsan best. Should be given in pre-critical period when temperature is rising, not when temperature is falling or in apyrexia, or relapses will ensue. If salvarsan compounds are injected when crisis is imminent grave toxæmia is precipitated. Albuminuria is no contra-indication to salvarsan treatment.

Arsant (salvarsan compound in which two arsenic atoms are replaced by antimony) recently recommended.

Arsenic-fastness rapidly acquired by spirochætes.

Collapse and fall of blood pressure with subnormal temperature following crisis counteracted by strychnine, intrarectal salines, injections of adrenaline and ephedrine.

Penicillin specific. Initial dose 1·5 mega units, 40,000 every three hours for 60 doses. Now recommended in combination with salvarsan.

Terramycin (oxytetracycline), by mouth or by intravenous route (0·5 gm. daily for 5 days) recommended, especially in infections with *Sp. persica* resistant to penicillin and arsenical compounds.

Prophylaxis.—In louse-conveyed form: anti-louse measures on approved lines. In tick-borne forms: measures based on habits of *Ornithodorus*. In Central Africa: old camping sites and native huts avoided. Bedsteads of native manufacture should not be used. If the traveller has to sleep on ground he must be well protected by mosquito-nets; night-lights scare away ticks. Huts constructed with space of 8–10 in. between walls and ground. Floors cemented. A deep trench round building filled with wood-ash keeps away ticks. Native children frequently act as reservoir of infection. **Gammexane** (benzene hexachloride) in water dispersible powder is lethal to these ticks.

Prophylactic inoculation.—Vaccine: cultures of spirochætes from initial attacks and relapses incubated at 37° C. for 3 days and kept at room temperature for 16 days: 3 injections of 1·0, 1·5 and 2·0 c.c. at 3-day intervals. Possible to produce immunity.

LEPTOSPIROSIS

Infection of blood and viscera with delicate spirochætes (leptospiræ).

Infectious Jaundice.—Weil's Disease: Spirochætosis Icterohæmorrhagica. A severe fever, especially in sewer workers, caused by *Leptospira icterohæmorrhagiæ*, with jaundice and enlargement of liver. Reservoir: rat. Canine epidemic gastritis (Stuttgart disease), or canine typhus, resembles Weil's disease and has been found increasingly common in man. Dog reservoir and may, although healthy, harbour *L. icterohæmorrhagiæ* and *L. canicola*. Serum of 27 per cent. healthy dogs agglutinates leptospiræ. *Canicola* fever found to be widespread in Holland, Germany and now recognized in England.

GEOGRAPHICAL DISTRIBUTION

World-wide, especially Japan; also England, France, Germany. Common in Holland, W. Africa, Congo, N. Africa, Mediterranean area, Egypt, Abyssinia, Andaman Islands, Malaya, Dutch E. Indies, United States, Guianas, Brazil, Peru, Argentine.

Epidemiology.—Japan: September–November. Europe: summer months. Leptospira is common harmless parasite of wild rats, mice and dogs, found in kidneys and excreted in urine. Abundant in polluted water.

Most common in farmers, miners, sewer workers, workers in fish factories; in Holland, in bathers in canals. Cane-cutters in Queensland.

Slime fever.—Mild form, in summer in Germany. Common disease of dogs, foxhounds, foxes, silver foxes, leopards, and other carnivora which eat rats.

ÆTIOLOGY

L. icterohæmorrhagiæ in blood, urine, C.S.F. and sputum. Spiral filament with wide flexures, the individual spirals in close apposition (20 μ by 0·25 μ—average 6–12 μ), demonstrated by dark-ground illumination and Fontana's strain. Rapid movements, one end straight, the other hooked. Progress by rotating posterior hook. Difficult to demonstrate in human blood, but easily found in guinea-pigs. In sections (especially of liver) by Levaditi's silver-nitrate impregnation. Cultured on blood-agar, also chorio-allantoic chick membrane. Serological races recognized—status uncertain ; dog strain : *L. canicola* (Holland), *L. grippo-typhosa* (E. Europe and Russia). In Queensland, *L. australis* A and B; many strains in Malaya. Differentiated by delicate Rieckenberg reaction. Rats infected : 32·4 per cent. Japan ; 56 per cent. Holland ; 4 per cent. sewer rats, London. Dogs : 6 per cent. in Sumatra. Guinea-pigs susceptible ; puppies, rats and monkeys less so. Injected intraperitoneally with 3–5 c.c. of blood, animals die with intense icterus on 10th day.

PATHOLOGY

Liver enlarged +. Gall bladder distended with bile. Both icterus and hæmorrhages ascribed to interference with prothrombin production in liver. Spleen enlarged with soft, diffluent pulp. Microscopically, cellular degeneration and focal necrosis ; fatty degeneration not so advanced as in acute yellow atrophy. Leptospiræ interstitial and intracellular. Enlargement of lymph glands. Hæmorrhages into kidneys. Petechial hæmorrhages into stomach, duodenum and lungs. Secondary anæmia : r.b.c. 3 million. Great reduction in blood platelets.

In inoculated guinea-pig : hæmorrhages into lungs form " butterfly patches."

CLINICAL FEATURES

Incubation period : 5–6 days. Onset : acute, rigors, vomiting, headache, diarrhœa ; then fever, thirst and aching. Characteristic intense injection of conjunctiva (? primary invasion by leptospiræ). Injection of palate ; agonizing limb pains ; paræsthesia of gastrocnemii. Temperature 103–105° F. (39·5–41° C.), falling by lysis on 10th or 11th day. Secondary terminal rise associated with excretion of leptospiræ from urinary tubules. Urine : albumin, bile, casts and occasionally r.b.c. Blood urea + before 10th day. Leptospiræ may persist in urine and be scanty in blood. Icterus in 50 per cent., 48–82 hours from onset ; jaundice progressing deeper till 9th to 10th days. Skin : orange-coloured, pruritus +, morbilliform and erythematous rashes; purpura indicates bad prognosis. Herpes labialis often. Also hæmorrhages into conjunctivæ, skin or mucous surfaces. In acute forms : black hæmorrhagic vomit and hæmaturia. Fæces pale.

Bradycardia in later stages ; blood pressure reduced ; polymorphonuclear leucocytosis, later lymphocytosis. Liver : enlarged ; gall bladder distended and tender. Splenomegaly exceptional. Inguinal and axillary lymphatic glands enlarged.

Convalescence in 3rd week. Occasional short recrudescences. *After fever*, allergic phenomenon, occasionally.

Typhoidal, uræmic and meningeal forms. In meningeal : C.S.F. under increased pressure and contains albumin and leptospiræ ; leptospiral meningitis ; fatal cases with paraplegia. Meningeal irritation specially common in *L. canicola* infections—resembles lymphocytic meningitis.

Complications : epistaxis, melæna, hæmoptysis, deafness, iritis and irido-cyclitis. Sequelæ : anæmia and debility ; alopecia. Mortality may be 18 per cent.

DIAGNOSIS

Blood : dark-ground illumination for leptospiræ, better by triple centrifugation. Blood (6 c.c.) injected into peritoneal cavity of guinea-pig—also urine after 12th day. Blood filaments often mistaken for leptospira. Agglutination test, with cultures of leptospiræ, 1 : 500–1 : 30,000 positive. Agglutinins in blood 6–10th day; persist for 22 months. Macroscopic agglutination also useful. Dark-ground illumination shows up agglutination. Living cultures preferred by Schüffner. Complement fixation reaction useful. Rieckenberg test (adhesion phenomenon). Urine gives green reaction with 2 drops acetic acid; also yields leptospiræ by centrifugation up to 40th day. High blood urea (200–300 mgm.). Van den Bergh reaction biphasic. Leptospira present in urine also by dark-ground illumination.

Differential diagnosis.—From yellow fever (difficult on clinical grounds), infective hepatitis, syphilis of liver, relapsing fever and malaria. From Heyd's syndrome—or hepatorenal failure with high blood urea. Hess' occlusion test is decisive. In leptospirosis a petechial rash is alway present above the constriction.

TREATMENT

General lines. Intravenous injection of glucose and saline. Diet liquid. Spirits of camphor for pruritus. *Penicillin* now considered most successful treatment in 40,000 units with an average of 1·5 mega units by continuous intramuscular drip ; given early before damage to liver or kidneys has taken place. Dramatic improvement in 36 hours.

Specific antiserum : 20 c.c. intravenously at intervals of several hours for 4 days ; for average adult man 60 c.c. daily. Convalescent serum also beneficial.

Prophylaxis.—Measures against infected rats, especially contamination of food. Avoidance of abrasion of hands in sewer workers and miners. Avoidance of infected water and canals by swimmers. " Crawl stroke " dangerous.

SEVEN-DAY FEVER

Autumn Fever—Japan. A short fever in summer months resembling infectious jaundice.

Geographical Distribution.—Especially Japan, also India and Dutch E. Indies.

Ætiology.—A leptospira (*L. hebdomadis*) distinguished from *L. icterohæmorrhagiæ* by serological reactions. In blood in small numbers, mainly in urine.

Reservoir host in Japan: vole—*Microtus montebelloi*. Guinea-pig susceptible to inoculation.

Clinical Features.—Conveyed by bite of field voles. Fever accompanied by conjunctivitis, muscle pains, lymphadenitis, albuminuria, leptospiræ in urine. Mild fever of 7 days' duration. No icterus; slight leucocytosis.

Diagnosis.—By serological tests and by demonstration of leptospiræ in urine. Differential diagnosis from infective hepatitis, rat-bite fever and especially dengue. Much confusion with latter; dengue rash distinctive.

Treatment.—Mild disease: Penicillin treatment.

RAT-BITE FEVER

Sodoku (Japan). Acute fever caused by *Spirillum minus* by bite of rat, sometimes cat or ferret.

Geographical Distribution.—Mainly Japan, but also in England, Germany, Italy, U.S.A., E. Africa, Australia.

Ætiology.—*S. minus*: small spirillum, differs in size from spirochætes (1·5–6 μ); has pointed extremities ending in flagella and 3–4 regular curves. Difficult to demonstrate in blood by dark-ground illumination, but can be found in exudate near bite and in aspirated juice from lymphatic glands. Moves rapidly, like vibrio.

After inoculation of white mice, organisms are demonstrated in blood in 7 days. Guinea-pigs and monkeys also susceptible. Probably identical with *S. muris*, occurring naturally in mice and rats. Often forms agglomeration 40–50 μ in diameter. Cultivated with difficulty on inspissated horse serum.

Some cases are due to *Streptobacillus moniliformis* "Haverhill Fever." Epidemic and may be milk-borne. May be conveyed by bite of laboratory rat, wild rats or other animals (cats). Incubation period 5 days. Wound heals promptly. Serum agglutinates *S. moniliformis*. Curable with penicillin. Arsenicals of no value.

Pathology.—Fatal cases rare. Hyperæmia of cerebral cortex and increase of pressure in C.S.F. Spleen enlarged, liver hyperæmic, lung hæmorrhages. In guinea-pigs and rats: swelling of lymphatic glands and spleen.

Clinical Features.—Incubation period, 1–60 days. Site of bite: inflamed cicatrix, with surrounding œdema and sometimes necrosis, lymphangitis and lymphadenitis. Rigors and malaise, temperature 103–104° F. (39·5–40° C.). Crisis at third day with profuse sweats = primary attack. Quiescent period of 5–10 days; then numerous relapses. Usually characteristic papular purple rash (may be urticarial or nodular) on chest and arms. Reflexes increased. Pains in muscles and joints, hyperæsthesia and œdema. In severe cases, delirium and coma. Moderate leucocytosis (15,000).

Diagnosis.—By history and occurrence of bite. Blood examination by dark-ground illumination, also exudate from bite, stained by Giemsa. Serum agglutinates spirillum in low dilutions. Usually pseudo-positive W.R.

Differential Diagnosis from relapsing fever, trench fever, nephritis (urticaria + œdema of face).

Treatment.—Salvarsan and neosalvarsan, 0·4–0·6 gm., specific; but now superseded by penicillin: equally effective for *Streptobacillus moniliformis*. Streptomycin and terramycin recommended. Former 0·5 gm. twice daily suffices; latter 2 capsules every six hours for one day and 1 capsule at similar intervals on the next.

Prophylaxis.—Extermination of infected rats.

YAWS (FRAMBŒSIA)

Sp. = spirochæte; Y. = Yaws).

A disease closely resembling syphilis, but confined to tropical countries. Organism: *Spirochæta pertenuis*, morphologically identical with *Sp. pallida*, also known as *Treponema pertenue*. Causes a more benign disease and is non-venereal.

GEOGRAPHICAL DISTRIBUTION AND EPIDEMIOLOGY

Relationship to syphilis uncertain, probably primitive old-world form; syphilis introduced after discovery of New World. Widespread throughout most tropical countries: tropical Africa, West Indies, S. America, Ceylon, Pacific Islands, Papua, East Indies, Malay States and China. Epidemic and endemic at present in W. Africa, Kenya, Tanganyika and Uganda. Highly contagious through breach of skin surface. Possibly carried by flies; in Jamaica oscinid fly (*Hippelates pallipes*) has been suspected. Auto-inoculation commonly practised in W. Indies. *Neither hereditary nor congenital.* Mother may be infected from child; congenital transmission unknown. No age exempt; most cases before puberty (child disease). Males more affected. Limited to tropics; does not spread to temperate zones. Y. is a rural disease: syphilis urban, especially in Haiti and Philippines. Native races show greater susceptibility. Many resemblances to *Bejel* (childhood syphilis of Arabs). There appears to be some reciprocal immunity between Y. and syphilis. The latter was unknown in Fijians in whom Y. was widespread. Since disappearance of Y. with mass therapy, syphilis is becoming increasingly common.

ÆTIOLOGY

Sp. pertenuis in skin lesions, or in serum from papules, examined by dark-ground illumination, stained by Giemsa, or Indian-ink methods. Found in spleen, lymphatic glands and bone marrow. Rabbits and monkeys susceptible. Higher apes reproduce picture of human disease. Cultivation difficult; has been effected on solidified horse serum. Testicular inoculation in rabbits produces lesion similar to syphilis; granular or finely nodular peri-orchitis; shorter incubation period than syphilis.

PATHOLOGY

No visceral changes, absence of endarteritis, thickening of epidermis, degeneration of epithelial cells, later hyperkeratosis. Papillæ vascular, infiltrated with lymphocytes and plasma cells, also giant cells.

CLINICAL FEATURES

Primary Stage.—Incubation period: 3–4 weeks, granuloma or papule (1–7 cm.)—" frambœsoma "—at site of abrasion or scar on buttock, knee, leg, arm, breast, lip or inner canthus of eye—never on scalp; breasts of nursing mothers and mouths of babies; often on hip or elbow in native women carrying children; may be single or multiple, lasting 3–4 months. Malaise, rheumatic pains, pyrexia, bone pains, lymphadenitis, W.R., and Kahn + 3–4 weeks after appearance of primary lesion.

Secondary Stage.—Three months after primary. Eruption, skin harsh, dry, fufuraceous desquamation, then minute papules. Yaw, or frambœsia, of varying size *commences round primary sore*, " mother and daughter yaw "; itching +. Pleomorphic, roseolar or resembling squamous syphilide. Lesions symmetrical—auto-inoculation—at angles of mouth, axillæ, arms and inguinal region, *never on mucous surfaces*. Y. papule: rounded excrescence, encrusted, hemispherical, or depressed, may be circinate. Inspissated serum forms crust of yaw; spirochætes +. Y. insensitive, attains maximum in 2 weeks. Papular form: acuminate papules. On subsidence, pigmented spots remain, sometimes lichenoid eruptions as in syphilis.

Tertiary Stage.—Y. ulceration at site of secondary lesion may coalesce, involving leg or ankle. Serum W.R. and Kahn +. C.S.F. negative; no cellular changes. Dactylitis common with onychia and atrophy of nails. Foot yaws—**crab yaws**—very painful subdermal on sole of foot; dermis splits in radiating fashion. **Gangosa:** ulcerous rhino-pharyngitis of palate with destruction of nose, associated with bone lesions. **Goundou** (especially in children): symmetrical hyperostosis of nasal bones, headache, sanguino-purulent nasal discharge. Swellings may enlarge and obstruct vision. May also be diffuse hyperostosis of superior maxilla.

Hard palate often affected. **Periostitis, osteitis and epiphysitis.**—Circumscribed painful periosteal nodes on radius, ulna and tibia. Diffuse osteitis causes sabre-shaped deformity of long bones, especially tibia (" boomerang leg "). Rarefying osteitis causes spontaneous fracture. Periostitis of clavicle noted. **Juxta-articular nodules.**—Fibrotic tumours, size of small orange, on olecranon, lower end of femur, etc. **Skin lesions.**—Depigmented patches on hands, feet and ankles are characteristic ; elephantoid limbs result from scar tissue. Synovitis and ganglion frequent. Nerve manifestations as in syphilis, unknown.

Immunity.—After secondary stage, but not permanent.

Sequelæ.—Aneurysm of aorta, neurological manifestations described, but very doubtful.

DIAGNOSIS

On clinical grounds ; and demonstration of *Sp. pertenuis.*

Differential diagnosis.—From syphilis always difficult : Hutchinson's notched teeth, interstitial keratitis and nerve deafness are absent. Y. always non-venereal. From Bejel sometimes difficult ; this is spread by contact and causes lesions of buccal mucosa and produces circinate lesions of soles of feet, hyperkeratosis and depigmentation of dorsum of hands. Meningo-vascular lesions of brain are not uncommon in children.

TREATMENT

Reaction to intravenous or intramuscular salvarsan, neosalvarsan, etc., immediate and striking. Also bismuth-sodium *tetra*-bismuth tartrate (sodium bismuthyltartrate, or Sobita). *Combined neo-bismuth treatment* : alternating weekly injections as in syphilis. *Penicillin* reported favourably, especially in primary and secondary stages—large doses, 1–2 mega units. Less effective in tertiary. Procaine penicillin superior, more slowly absorbed, injections less frequent. First day 4 c.c. (1·2 mega units), then one daily for six days or 2 c.c. twice weekly for three weeks. Penicillin aluminium monostearate (P.A.M.) preparation now recommended. Chloromycetin, aureomycin and terramycin have also proved satisfactory, especially latter when given intramuscularly.

Prophylaxis.—Isolation and segregation of affected. Mass treatment of natives now carried out. Nutrition essential.

PINTA (Carate)

A spirochætal skin disease characterized by peculiar depigmented patches.

Geographical distribution.—Tropical America, especially along rivers, Mexico to Peru and Chile.

Ætiology.—*Spirochæta*, or *Treponema, carateum* (*Sp. herrejoni*) closely resembles *Sp. pallida*, found in skin and lymph glands. Stained by Giemsa or Fontana, shows flexible cylindrical form with pointed ends, 10–12 μ in length, with turns 0·6–1 μ wide. Attempts to cultivate it have so far failed.

Clinical Features.—Eruption symmetrical, readily mistaken for syphilis ; lesions of slow evolution with atrophy ; W.R. and Kahn + ; responds to anti-syphilitic treatment. Incubation period : 7–20 days; initial papule. Hyperpigmented spots alternate with vitiliginous depigmented patches which may become white or blue (slaty or leaden), usually on face and extremities, often over bony prominences, knuckles and malleoli. Pinta is contagious and affects all ages and both sexes, usually in adults, 15–25, associated with hyperkeratosis of palms of hands and soles of feet. Small patches on mucous membranes. Onchogryposis or pigmentation of nails frequent.

Diagnosis.—Biopsy of skin and demonstration of spirochæte by scrapings and dark-ground illumination.

Differential diagnosis.—Especially from syphilis, yaws, leprosy, erythrasma, ringworm and pityriasis versicolor.

Treatment.—With salvarsan, penicillin and bismuth as for syphilis.

CHAPTER III

RICKETTSIAL DISEASES

THE TYPHUS GROUP

Comprises numerous closely-allied fevers, mostly characterized by sthenic character and rash, caused by infection with *Rickettsia*.

TABLE III

TYPHUS FEVERS

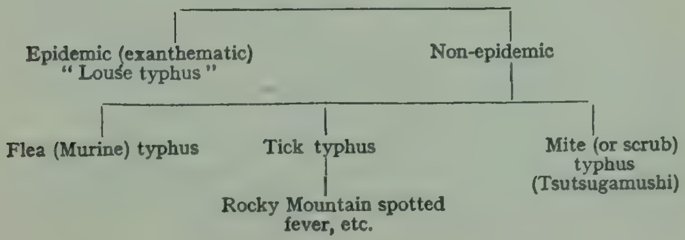

TABLE IV
CHIEF FEATURES OF TYPHUS GROUP

Type	Rickettsia	Geographical Distribution	Insect Vector	Vertebrate Reservoir	Weil-Felix Reaction Proteus		
					OX19	OX2	OXK
1. Exanthematic typhus. Louse typhus. Brill's disease.	*R. prowazeki*	Europe, N. America, N. Africa and E. Belgian Congo, Asia Minor, Persia, N. China, Mexico	Louse (*Pediculus humanus*)	Man	+++	+	–
2. Endemic (murine) typhus. Flea typhus.	*R. prowazeki* var *mooseri* or *muricola*	World-wide	Rat Fleas (*Xenopsylla cheopsis* and *X. astia*)	Rat, (Squirrel, shrew)	+++	+	–
3. Trench fever	*R. quintana* var *wolhynica*	Central Europe	Louse (*P. humanus*)	Man	Negative		
4. Tsutsugamushi Scrub typhus	*R. tsutsugamushi* (*orientalis*)	Japan, Formosa, Malaya, Java, Sumatra, N. Guinea	Mites (Larvæ of *Trombicula akamushi. deliensis*) *hirsti, scutellaris*	Rats and field voles	–	–	+++
5. Rocky mountain spotted fevers, E. and W. forms	*R. rickettsi*	U.S.A.	Ticks (*Dermacentor andersoni. D. variabilis*)	Woodchuck, ground squirrel, gopher and other rodents	+	+	+
6. Fièvre boutonneuse	*R. rickettsi* var *conori*	Mediterranean	Tick (*Rhipicephalus sanguineus*)	Dog			
7. Tick typhus African tick typhus	*R. rickettsi* var *pijperi*	S., E. and W. Africa, S.E. Asia, Queensland	Ticks (*Hæmaphysalis leachi*, etc.)	Dog	+	+	+
São Paulo rural typhus	*R. rickettsi* var *braziliensis*	S. Brazil	Tick (*Amblyomma cajennense*)	Opossum. Wild dog.	?	?	?
8. Q fever (Query fever)	*R. burneti*—(*R. diaporica*)	Australia, U.S.A., Europe, England (probably widespread)	Ticks (*Hæmaphysalis humerosa, Dermacentor andersoni*)	Bandicoot (*Isoodon torosus*) (Australia) In America and Europe no arthropod host, but probably dust infection.	–	–	–
9. Rickettsialpox	*R. akari*	U.S.A.	Mouse mite (*Allodermanyssus sanguineus*)	Mouse (*Mus musculus*)	– (complement fixation +)	–	–

Cycle of development of R. prowazeki in louse.—Multiplies in midgut, lumen and intracellular epithelial cells ; distended cells—easily recognizable—rupture so that rickettsia appears in fæces ; causes death of louse in 10 days. Infection conveyed to man by louse fæces through skin abrasions or conjunctiva. Louse fæces infective for 66 days ; no hereditary infection. *R. prowazeki*, var *mooseri*, or *muricola*, normally transmitted from rat to rat by rat-louse (*Polyplax*), and by flea, *Xenopsylla cheopis*. Cycle similar to that in louse ; does not harm flea. Flea typhus regarded as pristine form; may be converted into epidemic louse typhus. *Rickettsia prowazeki*, *R. mooseri*, *R. conori* (boutonneuse) S. African tick-bite fever and Kenya tick typhus, *R. rickettsi*, *R. akari*, *Coxiella* (*Rickettsia*) *burneti*, *R. tsutsugamushi* and *R. quintana;* all except last two multiply or survive in the hæmolymph of the meal-worm (*Tenebrio molitor*) and in the tick (*Ornithodorus moubata*). All multiply in the hæmolymph of the body louse and can be passaged through the lice by intracoelomic inoculation. All except *R. tsutsugamushi* and *R. rickettsi* can be passaged repeatedly from louse to louse by rectal inoculation.

Ticks.—cycle of development of *R. rickettsi* and allied organisms in ticks similar, but more widespread. Rickettsiæ intracellular and intranuclear in all tissues, invading ovaries ; infection therefore hereditary. Infection in salivary glands and conveyed by bite.

Mites.—Rickettsiæ are found in the body-cavity of the adult mite—*Trombicula akamushi*—and in the salivary glands of the infective larval stage—*Microtrombidium*—and persist from one generation to the next, a period of 30 days. Infection probably contracted by adult and transmitted to larva. Larva itself requires only one single meal of blood to complete development.

In human tissues rickettsia appears as small bacilli or cocci ; diploid and coccoid forms common.

Cultivation not possible on solid media, but grows on chorio-allantoic membrance, especially in duck eggs. In embryo and in tissue culture produces foci in 5 days. Pure strains of *R. prowazeki* obtained by intrarectal injection of louse with infective material.

N.B.—**Exanthematic typhus** is characterized by invasion of endothelium and mesothelium by rickettsiæ, distension of cytoplasm of host cells without affecting nuclei. **Tick-conveyed typhus** is characterized by thrombo-necrosis of arterioles and venules ; massive infection of nuclei also in those of infected ticks, and especially in tissue culture. Hereditarily transmitted.

Neill-Mooser reaction.—Distinctive reaction in guinea-pigs inoculated with typhus blood, especially in murine type; redness and swelling of scrotum; typical lesions in scrotal vessels and endothelium of tunica vaginalis. *R. rickettsi* gives + reactions; also 70 per cent in. *R. prowazeki.*

Serological reactions in differentiation.—Weil-Felix reaction, agglutination with culture of *Proteus vulgaris* (X 19): variations XK, X2 and X3. Agglutination distinctive for exanthematic and murine typhus ; XK for tsutsugamushi (scrub typhus). Tick-borne forms intermediate. *O* variants of culture used—hence prefix O, *e.g.*, OX 19. Serum diluted, macroscopic method of agglutination. Dried blood may also be used. Agglutination tests with antigens prepared from cultures of rickettsiæ now preferred. Complement-fixation tests with similar antigens are more reliable and have become a routine procedure.

LIST OF TICK AND MITE VECTORS OF RICKETTSIAL DISEASES

1. N. America.—*Amblyomma americanum, A. cajennense, Dermacentor andersoni, D. variabilis, Allodermanyssus sanguineus.*
2. S. America.—*Amblyomma brasiliense* and *A. cajennense.*
3. Europe and Asia.—*Dermacentor nuttalli, D. silvarum, Hæmaphysalis cincinna, Hyalomma dromedarii, H. excavatum, H. savignyi, Rhipicephalus appendiculatus, R. evertsi, R. simus* and *Allodermanyssus sanguineus.*
4. Africa.—*Amblyomma hebræum, Hyalomma dromedarii, H. excavatum, H. savignyi, Rhipicephalus appendiculatus, R. evertsi, R. simus* and *Allodermanyssus sanguineus.*
5. Australia and Pacific Islands.—*Dermacentor variabilis, Ixodes holocyclus, Trombicula akamushi—T. deliensis* complex.

Treatment.—Remarkable effects of 3 broad-spectrum antibiotics shown in table below:

AVERAGE DURATION IN DAYS OF FEVER AFTER FIRST DOSE

	Typhus Group Fevers					
	Louse-Borne	Flea-Borne	Mite-Borne	Trick-Borne		Q Fever
				American	African & Indian	
	*I & III	II	IV	V	VI & VII	VIII
Chloramphenicol (Chloromycetin)	2	3	2	4	3	3
Chlortetracycline (Aureomycin)	3	2	2	3	3	5
Oxytetracycline (Terramycin)	4	3	2	4	2	3

* Numbers refer to groups, see Table IV.

Dosage schedule for all three drugs is initial loading dose of 50–60 mgm./kg. body-weight followed by the same daily doses given in 3 or 4 divided doses till defervescence. Side effects, nausea, vomiting or diarrhœa occasionally.

I. EPIDEMIC OR EXANTHEMATIC TYPHUS

Acute fever lasting 14 days, terminating by crisis ; pyrexia remittent, petechial rash on fifth day.

GEOGRAPHICAL DISTRIBUTION AND EPIDEMIOLOGY

World-wide, common in E. Poland and Russia 1917–23 (over 30 million cases, 3 million deaths), N.W. Frontier of India, N. Africa, Belgian Congo, Abyssinia, Central and S. China, Manchuria, Mexico, Gold Coast, E. Africa, Philippine Islands. Usually a disease of dirt and bad sanitation, in autumn and winter months, in conditions of overcrowding favourable to louse transmission. Brill's disease, first described in Jewish immigrants in New York, probably mild form of typhus or possibly relapse of original rickettsial infection.

ÆTIOLOGY

R. prowazeki: specific virus conveyed by lice (*P. humanus corporis* and *capitis*), filterable from blood plasma and blood platelets during first five days. Blood infective for guinea-pigs and monkeys. Infection conveyed by louse fæces inoculated by scratching. Inhalation of dried infected louse fæces is probably capable of causing infection.

Transmission.—(*see* p. 73).

Bionomics of louse.—(*see* p. 58).

Prophylaxis.—(*see* p. 76).

PATHOLOGY

Blood dark, does not clot. Toxic damage to liver and kidneys. Rash visible post-mortem ; caused by localized necrosis of walls of blood vessels forming typhus nodules (collections of lymphocytes and plasma cells in adventitia) in vessels of skin, C.N.S. and myocardium. Areas of skin necrosis and gangrene. Hæmorrhages in conjunctivæ. Spleen enlarged and diffluent. Hypostatic congestion of lungs. Mesenteric glands enlarged. Red marrow hyperplastic and converted into yellow marrow ; little increase in myeloid elements.

CLINICAL FEATURES

Incubation period : 4–14 days ; onset : 2 days. Headache, nausea, delirium, convulsions. T. 104° on 3rd day ; face and eyes congested; stuporose drunken expression, tongue coated brown, epistaxis frequent. Urine: cloud of albumin, increase of urea and chlorides. Rash on 5th day on abdomen, inner aspect of arms, then chest, back of trunk, face (rarely), palms of hands, soles of feet ; pleomorphic, mulberry, petechial "subuticular mottling" ; papular or roseolar ; sometimes may resemble flea or louse bites ; persists 10 days, fades slowly. In partially-immune population rash may be slight, even absent. In native races detection is difficult, but aided on upper arm by Bier's congestion method by tourniquet. Blood : moderate leucocytosis 12,000—15,000 ; mononuclear increase. Pseudopositive W.R. before crisis. Pulmonary complications or bronchitis on appearance of exanthem.

" Typhus state " ; face flushed earthy blue (*facies typhosa*), tremors. Skin : " gun washings " odour. Spleen enlarged. Muscular fibrillations. Eyes " ferrety " ; in very severe cases pupils " pinpoint." After two weeks' remittent pyrexia T. falls by crisis or rapid lysis on 13th or 14th day. Death from exhaustion or cardiac failure. Mild form lasts 10 days, frequent in children. Mortality varies : 60 per cent., especially in young, aged, and pregnant women. Fulminating cases : *Typhus siderans.*

Complications and sequelæ.—Often with relapsing fever (*q.v.*) constipation, abortion in pregnancy. Parotitis, noma, bronchopneumonia, gangrene of lungs. Sores on lips and teeth, gangrene of limbs or skin. Paralyses of limbs, hemiplegia (typhus nodules in brain), mania, dementia.

DIAGNOSIS

Weil-Felix reaction positive in low dilutions (macroscopic) 5th day, maximum 8th–21st day ; 1 : 2,500 for 60 days. (Co-agglutination of *S. typhosa* sometimes.) New method with dried blood and emulsions of OX 19 coloured with methylene blue. Relationship of *B. proteus* to disease uncertain ; may occasionally be isolated from urine. Skin biopsy particularly useful, shows typical periarteritis nodosa due to thrombosis of smaller vessels.

Differential diagnosis.—From measles, typhoid, relapsing and cerebrospinal fevers, occasionally S.T. malaria ; plague in early stages ; septic meningitis. Difficult from tick-typhus. *From typhoid and paratyphoid* : temperature curve ; skin eruption ; leucopenia in typhoid, leucocytosis in typhus. Roseola in paratyphoid may simulate typhus rash; nervous signs and symptoms less severe. Roseola on palms and soles not found in typhoid or paratyphoid.

TREATMENT

Broad-spectrum antibiotics—chloromycetin, aureomycin and terramycin—all specific. By mouth in capsules of 0·25 gm. each. In severe cases, intravenous or intramuscular injections of 0·1 gm. per c.c. in propylene glycol. Dose 1·5–4 gm. daily for 2–3 days.

Good nursing essential ; bedsores to be avoided. Alcoholic stimulants and tinct. digitalis for heart. Lumbar puncture relieves delirium and cerebral symptoms. Convalescent serum injection (20–50 c.c.) disappointing.

Prophylaxis.—Anti-louse measures, cresol bath, naphthaline soap, superheated steam for clothes. Quarantine period 15 days. Anti-louse powder contains 10 per cent. DDT. Speed great advantage. Individual can be treated fully clothed. Three treatments at weekly intervals eliminate all lice and nits. Large numbers can be handled by specially trained teams. For head lice powder can be applied direct to head and neck. 30–40 persons can be dusted in an hour. Powder remains active and will continue to kill lice and other insects for 2–3 weeks. *Impregnated clothing.* Angola shirts impregnated at rate of

0·1 per cent. DDT weight for weight of garment, referred to as A/T and has proved most effective. When unwashed afford protection for 8 weeks, less so for 4 more. Washing destroys efficiency of DDT after third time. Powder insufflated by some kind of blower in loosened clothes. Best blowers are "Dobbin" or "Hudson" Dusters. Nozzle shortened to project 8 ins. beyond barrel. Insufflate powder, mixed with air, 1½–2 oz. per each person. Head covering treated first with arms extended. Delivery tube inserted into both sleeves and powder pumped in. Armpits and shoulders especially. Inserted in front of chest and sprayed laterally, then neck band and back, trousers, crutch and pubic areas. Coat laid on table, armholes and inside dusted. Trousers treated same way, powdering down seams and down both legs.

Prophylactic inoculation.—Not very satisfactory. Weigl's vaccine made from intestinal contents of infected lice mixed with formol saline. Cox's vaccine made from rickettsiæ grown on yolk sac of chick embryo; immunity transient. Other vaccines, made from lungs of mice, injected by intranasal route and from brains of infected mice, under trial.

II. MURINE TYPHUS, FLEA TYPHUS. (SHOP TYPHUS in Malaya.)

Regarded as endemic form of I and the starting point of epidemic outbreaks.

Geographical distribution and epidemiology.—World-wide, especially in Mexico, N. America, Palestine, Abyssinia, Malaya. Typhus rats common in Mediterranean. Seasonal incidence constant; majority of cases in summer and autumn. Twice as common in males as females. Negro less susceptible than European. Evidence that under certain conditions rat virus may be converted from rat-flea-rat cycle into man-louse-man cycle.

Ætiology.—Organism : *R. prowazeki*, var *mooseri*, or *muricola*, normally parasite of rat, is spread from rat to rat by rat louse or rat fleas (*X. cheopis* and *X. astia*) ; from rat to man when in contact. Endemic typhus found in vicinity of grain stores which harbour rats. Development and transmission of rickettsia through *Xenopsylla cheopis* described on p. 73. Rickettsia does not harm flea.

Clinical Features.—Symptoms resemble those of I, but milder in every respect. Mortality small (1·5 per cent.).

Diagnosis, Differential Diagnosis and Treatment.—Identical with I.

III. TRENCH FEVER

Five-day fever, Wolhynian fever, of primary importance in 1914–1918 War on Western Front, also in Poland, Russia, Macedonia, N. Italy.

Not seen since, though similar fever appeared in Weigl's laboratory amongst workers who had been feeding lice (1939) and in E. Prussia in second world war.

Geographical distribution and epidemiology.—Probably identical with Wolhynian fever recognized by Polish physicians before 1914. 800,000 cases diagnosed in France, 1914–1918, mostly in winter when lice prevalent. Group distribution consistent with migratory habits of louse.

Ætiology.—*Rickettsia quintana,* var *wolhynica,* conveyed by lice fed on trench fever patients as in I. Development in louse takes 5 days.

Clinical.—Incubation period 2–3 weeks. Initial febrile attack followed by relapsing pyrexia. Onset : sudden ; pain in back and legs. Spleen enlarged by one-third. No exanthem. Tenderness and pain in shins most acute and characteristic. *Sequelæ* few and mild ; usually tachycardia. Mortality nil, recovery complete.

Treatment.—By antibiotics as for other rickettsiases.

Prophylaxis.—DDT as in typhus.

IV. TSUTSUGAMUSHI. MITE TYPHUS

" Scrub typhus," acute endemic typhus ; initial eschar at site of bite of mite, *Trombicula akamushi.*

Geographical distribution and epidemiology.—Japan, Formosa, Korea, Malaya, Ceylon, New Guinea, Pescadores, Philippines, Indo-China, Hong Kong, Siam, Bombay, Queensland. Men more commonly affected than women, especially labourers, cane-cutters and workers on palm plantations in Malaya, particularly after floods and rainy season. In Formosa, April–November. In Japan winter scrub typhus known as " Shichito Fever."

Ætiology.—*Rickettsia tsutsugamushi* (*orientalis*) develops in *leptotrombicula,* or *microtrombidium*—larval stage of mite (*Trombicula akamushi*—in Sumatra, *T. deliensis* and ? *T. hirsti*). Infection conveyed in bite through salivary glands. Winter scrub typhus in Japan spread by *T. scutellaris.*

Reservoir host.—Wild rats, local varieties found infected with *R. orientalis* and mite is parasitic on them. *R. tsutsugamushi* transmitted to guinea-pigs and rabbits by intra-ocular inoculation.

Transmission.—Trombidiidæ—velvet mites—burrow under skin (harvest bugs). Adult trombicula in soil of infected fields ; 0·9 mm. by 0·5 mm. ; pale grey or red, with rudimentary eyes, four pairs of legs, anterior pair stout, two pairs of suckers on ventral surface. Larva leptotrombicula (*microtrombidium*), 0·4 by 0·25 mm. ; resembles harvest mite in appearance ; has three pairs of legs (hexapod) covered with minute plumose hairs. Larva of *T. akamushi:* bright vermilion, of *T. deliensis:* pale ochre. These mites do not suck blood but, on attaching themselves to the skin, inject a proteolytic ferment. The skin of the host becomes hardened and a tube (stylostome) is formed in which the mite lies and where it continues to imbibe fluid until it is replete. It is the reaction to this digestive fluid which causes the bite to itch.

Pathology.—Lesion at site of bite: coagulation necrosis; other lesions resemble those of I, except that widespread thrombotic lesions of peripheral blood vessels do not occur. Histologically, chief change is perivascular infiltration; intima secondarily attacked.

Clinical.—Bite of mite at first not noted; larvæ easily seen by magnifying glass with heads and bodies in skin. Incubation period: 4–10 days; malaise, frontal and temporal headache, then pain and tenderness in lymphatic glands of groin, axilla and neck. Eschar, 2–4 mm., surrounded by red areola, some lymphangitis. T., 104–105° F. Conjunctivæ injected. Bronchitis. Splenomegaly. Rash: 6th–7th day, dark red papules on forearms, legs, trunk—roseolar on face; less pronounced on upper arms, thighs, neck and palate; more pronounced than in I. Delirium, deafness. Primary ulcer heals in second week; temperature falls by crisis or lysis on 14th day. Complications and sequelæ as in I; pregnant women usually abort. Mortality: 20–30 per cent. in Japan: in Sumatra 15 per cent. *N.B.*—Uninfected mite bites may give rise to irritation at site and mild constitutional phenomena.

Diagnosis.—As in I; Weil-Felix reaction OXK (Kingsbury strain). Intradermal test with OXK also employed. Initial necrotic ulcer and lymphadenitis characteristic. Differentiate from other forms of typhus, measles and dengue.

Treatment.—Site of bite cauterized or excised.

Prophylaxis.—Mite-proof suiting for workers in infected fields; mite bites treated with disinfectant (Vleminckx's solution—sulphide of calcium); smearing clothes and exposed parts with dibutyl phthalate proved most successful in Burmese war. In Malaya chloromycetin fairly efficient prophylactic, 4 gm. weekly for a period of 4 to 6 weeks after volunteers had been exposed for 6 days in hyperendemic areas of scrub typhus (Smadel). Aerial photography used for identification and delineation of areas of jungle in which scrub typhus constitutes a hazard. Residual insecticides, especially aldrin and dieldrin, effective in Malaya in controlling the trombiculid vectors of scrub typhus.

V. TICK TYPHUS—ROCKY MOUNTAIN SPOTTED FEVER

A typhus fever supervening on the bite of ticks, *Dermacentor andersoni* and *D. variabilis* in U.S.A.

Geographical distribution and epidemiology.—Originally thought to be confined to Western States—Idaho, Wyoming, Utah. Now two forms known: Eastern and Western; latter more severe.

E. reported from 32 States (exceptions : Maine, New Hampshire, Vermont, Connecticut, Wisconsin). W. as above ; also in Nevada, Oregon, Colorado, New Mexico. New focus now in Colombia, 2,000–4,000 ft. Magdalena basin. Sharply-defined limited areas in valleys, near foothills. *D. andersoni* prevalent March–June in W. ; *D. variabilis* ("dog tick") March to December in E. Latter infection commoner in women and children ; ticks brought into houses by dogs.

Ætiology.—*R. rickettsi* introduced by bite of tick, *D. andersoni* (wood-tick) in W., and *D. variabilis* (dog-tick) in E. Only adult form attacks man. Proportion of infected ticks small.

Transmission.—*R. rickettsi,* parasite of tick ; period of invasion after feeding : multiplication of rickettsiæ in body of tick and conversion into tick virus. Ticks infected when animal hosts come out of hibernation.

Animal reservoir hosts. — Columbian ground squirrel (*Citellus columbianus*) and woodchuck (*Marmota flaviventris*) burrow in birch woods, hibernate ; infection maintained amongst rodents by "rabbit tick," *Hæmaphysalis leporosa. R. rickettsi* recently isolated from meadow mice (*Microtus pennsylvanicus*) in Virginia where patients contracted infection.

Ticks.—*Dermacentor andersoni* : yellow, with dark markings on cephalothorax ; very abundant ; adult in summer months attached to horses and wild animals, and feeds on man. Larvæ and nymphs on ground squirrels, etc., form reservoir of rickettsia. Female when engorged falls from host and deposits 7,000 eggs. Hexapod larvæ and nymphs engorge and fall to ground and moult. Whole cycle two years; adults can fast for two years. *D. variabilis* : widely distributed E. and N. America, resembles above. Larvæ and nymphs feed on small mice ; adult attacks dogs, animals, man.

Pathology.—As in I, especially "typhus nodules," splenomegaly, enlargement of lymph glands, *gangrene of prepuce and scrotum,* petechial skin hæmorrhages, subserous hæmorrhages in brain, heart, kidneys, lungs and adrenal cortex.

Clinical features.—Incubation period : 3–7 days. *No primary eschar,* otherwise as in I. Often icterus, splenomegaly. Rash 5th–7th day on wrists, ankles, trunk, scalp, hands and feet ; roseolar and petechial ; more florid than in I ; usually desquamates ; gangrene of fingers, toes and lobes of ears. Little evidence in support of separation of E. and W. typhus ; possibly rash of latter is more intense and widely distributed.

Mortality.—Montana 90 per cent., E. form 5–10 per cent.

Diagnosis.—In endemic areas not difficult, but differentiation from other forms of typhus not easy, except by history. Injection of blood into guinea-pigs produces Neill-Mooser reaction (p. 73). Weil-Felix reaction not so reliable (p. 73) ; feeble agglutination : OX19.

Treatment.—Nursing and general measures (*see* p. 76).

Prophylaxis.—On methods of transmission : extermination of ground squirrels and woodchucks ; systematic arsenical dipping of sheep and goats in epidemic areas to rid them of ticks. Dogs may be freed from *D. variabilis* by powdered derris root and especially by dusting powders containing DDT and gammexane (benzene hexachloride).

Prophylactic inoculation.—Vaccine made (Parker) by grinding up infected ticks in formol saline, standardized by protection tests in guinea-pigs. 1 c.c. for children, 2 c.c. for adults; has definite value in Montana.

VI. TICK TYPHUS. (FIÈVRE BOUTONNEUSE)

Tick-bite fever, Mediterranean, N. Africa. *R. rickettsi*, var *conori*, transmitted by dog-tick.

Geographical distribution and epidemiology.—Mediterranean, Marseilles, S. France, Italy, Portugal, Spain, Greece, Roumania, Guinea Coast, Senegal, Sierra Leone.

Ætiology.—*R. rickettsi*, var *conori*, develops in tick, *Rhipicephalus sanguineus*, as in V. Infection hereditary, also by tick-bite. Dog reservoir ; blood in endemic areas infective for man and monkey. Tick : common dog-tick of S. Europe, hard tick (Ixodidæ), brown, occurs all the year round ; cycle completed in dog kennel. Three hosts ; larvæ, nymphs and adults, drop off animal after engorging. Female lays 3,000 brown eggs which hatch at 25° C. (77° F.); larvæ immediately attach themselves to new host.

Pathology.—As in I ; no distinctive features.

Clinical features.—Distinctive primary sore (" tache noire ") at site of bite, size from pin's head to pea, not painful ; subsequent lymphangitis. Rash : 5th–7th day, profuse and nodular, especially on trunk and legs, otherwise resembles I.

Treatment.—(*See* p. 74).

Diagnosis.—On history and endemic zone. Neill-Mooser reaction in guinea-pigs +, Weil-Felix reaction rather indefinite (see p. 73). No cross immunity of blood between I and II.

Prophylaxis.—Dusting pet dogs with DDT powder to keep them free from ticks.

VII. TICK-BITE FEVERS OF S. AMERICA, E. AFRICA AND INDIA

Tanganyika, Kenya, S. Abyssinia ; resembles Fièvre boutonneuse, but is conveyed by bite of larval ticks, *Amblyomma hebræum*, *Rhipicephalus appendiculatus* and *Boophilus decoloratus;* in Cape Province, *Hæmaphysalis leachi*.

Amblyomma: small, ornate, with eyes, widely distributed on lizards and birds ; has three hosts of same species. *Rhipicephalus appendiculatus:* dog tick of S. Africa, resembles *R. sanguineus. Boophilus decoloratus:* cattle tick, not ornate, eyes present. *Hæmaphysalis leachi:* not ornate, eyes absent. In adult and larval stages on carnivora, especially dogs.

Small larval ticks climb on grass and attach themselves to man and animals, especially on veld ; not found on horses or domestic animals. Rickettsiæ found in Malpighian tubules of ticks. Emulsion produces disease in guinea-pigs and *slight* Neill-Mooser reation. Dog probably reservoir of infection for man.

Clinical.—Two forms described : (1) mild or abortive, (2) fully developed. In first : primary sore, adenitis and lymphangitis at site of bite. In second : in addition, fever for ten days with headache, stiff neck, conjunctivitis. Petechial rash on 5th day.

Diagnosis.—By Weil-Felix reaction (not clear-cut). OXK agglutinated in higher titre than OX19. Virus does not immunize against I or II.

Treatment.—(*See* p. 74).

S. American tick typhus, common in Brazil, resembles Fièvre boutonneuse. Rickettsia transmitted by *Amblyomma cajennense;* primary eschar, lymphangitis and adenitis, mortality 80 per cent. Weil-Felix not clear cut, agglutination with OX19, OX2, OXK. Natural reservoirs : opossum, domestic and wild dog and agouti.

Indian form.—Sporadic mild form of typhus in N.W. Frontier of India, from Lucknow and Simla Hills. Tick vector unknown at present.

VIII. Q. FEVER. (Q=Query)

Noted since 1935 in Queensland. Due to *Coxiella* (*Rickettsia*) *burneti*, now recognized to be identical with *R. diaporica*, widespread in West U.S.A. and there carried by tick, *Dermacentor andersoni.* Recently in outbreaks in Greece, Turkey, Italy, Switzerland, whole of Central Europe, England; increasingly common in U.S.A. Congolese " Red Fever " now shown to be exanthemic form of Q fever.

Geographical distribution and epidemiology.—Queensland and U.S.A. No relationship to season, most cases in meat workers and dairy farmers.

Ætiology.—*C. burneti* produces characteristic pathological effects on monkeys, mice and guinea-pigs. In mice : enlarged liver and spleen ; large number of rickettsiæ in intracytoplasmic colonies. Smallest of all rickettsiæ and filterable. Rickettsiæ cultivated on chick embryo. Reservoir host in Queensland : bandicoot (*Isoodon obesulus*), specially liable to laboratory infections. Transmitted to man by tick, *Hæmaphysalis humerosa*, in which rickettsiæ occur as natural infection. In U.S.A., *Coxiella burneti*, var *americana* (*diaporica*), has been isolated from ticks—*Ornithodorus turicata* and *D. andersoni*, also from spleen of infected merions in Morocco (*M. shawi*). Present in pulmonary cases in sputum and can be conveyed to mice and guinea-pigs.

Disease is very infectious in Europe and U.S.A. and is there probably conveyed by dust, not by droplet. Milk from cattle and goats may also convey infection. No evidence of any association with ticks in many areas. Widespread in sheep, goats, cattle and buffaloes. Isolated from tick *Hyalomma dromedarii* on Sudanese bulls in Egypt, also from fæces of sheep and from amniotic and allantoic fluids of these animals in N. Carolina and from tick, *Ixodes polocyclus*, in Queensland. In N. Africa associated under natural conditions with wild rabbits and tick *Ornithodorus erraticus* found infected.

Clinical.—Onset acute, sudden. Pyrexia ; defervescence 6th–9th day, sometimes 4th week. No rash or splenomegaly. Persistent headache; comparative bradycardia. In U.S.A. and Europe associated with pneumonitis. Mild illness; no fatalities.

Sera of animals experimentally infected with Australian and American strains agglutinate *C. burneti*. No cross immunity with V. Rickettsia present in human blood during fever and in urine in later stages.

Diagnosis.—Complement fixation test most reliable. Also made by isolation of organism in mice and guinea-pigs. Radiographs of lungs show evanescent diffuse opacities in central portion over hilum. Difficult to distinguish from appearances of atypical pneumonia. Pulmonary signs appear clinically in about 50 per cent. of cases.

Treatment.—(*See* p. 74).

IX. RICKETTSIALPOX

Described in New York in 1946—pox-like rash prominent feature and organism is *R. akari*, transmitted by mouse-mite, *Allodermanyssus sanguineus*. No positive Weil-Felix reaction, but complement fixation test is valuable: apparently a mild disease: no mortality; *chloromycetin* is curative.

BARTONELLOSIS

Bartonella and rickettsia resemble each other morphologically. *Oroya Fever* and *Verruga Peruana* are clinical manifestations of the same disease.

(A) OROYA FEVER (CARRION'S DISEASE)

Acute specific fever in Andes.

Geographical distribution and epidemiology.—Latitude : 9–16° S. ; elevation : 3,000 to 10,000 ft. Peru, Chile, Bolivia, Colombia. Hot, narrow ravines ; attacks travellers, engineers, etc.

Ætiology.—Rod-like bodies in r.b.c. and endothelial cells of lymphatic glands. *Bartonella bacilliformis* resembles *Theileria parva*—piroplasma—also *Bart. canis* of dog. Rod-shaped bacillary organism, 2 by 0·5 μ, with rounded and V-shaped forms stained by Giemsa; long trailing flagella shown by electron microscope. Cultivation on citrated blood and allantoic membrane of chick. Inoculated intradermally into monkeys, reproduces the disease. Experimental infection of squirrels in Carolina (*Sciurus carolinensis*) and a ground squirrel (*Citellus tridecimlineatus*) reported.

Transmitted by sandflies (*Phlebotomus verrucarum*) in Peru ; also *B. bacilliformis* found on tip of proboscis in sandflies caught in Peruvian verruga zone. Neill-Mooser scrotal reaction may be produced by inoculation of guinea-pigs with cultures of *B. bacilliformis.*

Pathology.—Liver degeneration and focal necrosis, hæmosiderin + ; spleen enlarged with necrotic areas ; lymphatic glands enlarged; histiocytes enclosing bartonella. Bone marrow proliferation, necrosis and endothelial macrophages. In advanced stage of the disease, *B. baccilliformis* found in endothelial cells in clusters.

Clinical.—Incubation : 3 weeks. Onset : insidious. Irregular, remittent pyrexia with severe pains. Liver and spleen enlarged and tender. Rapidly developing anæmia—r.b.c. down to 500,000 in 3–4 weeks ; polymorphonuclear leucocytosis, megalocytes. Pain in head, joints and bones. Most severe types resemble typhus. Terminal delirium; mortality 10–40 per cent. Secondary bacterial infections with members of the *Salmonella* group frequent and terminal.

Treatment.—Chloromycetin terminates primary infection and is effective especially against grave danger of salmonellosis which is the cause of a high percentage of deaths. The average total dosage is 17 grm. It is recommended for five days in divided dosage. The temperature declines within 24 hours during which time the bacillary forms of bartonella are transformed into coccoid forms before vanishing.

Prophylaxis.—DDT measures against sandflies as in other phlebotomus-conveyed diseases.

(B) VERRUGA PERUANA

A granulomatous eruption associated with hæmorrhages, fever and joint pains.

Ætiology.—Superficially verruga resembles yaws. Bartonella-like bodies in nodules ; probably local connective tissue infection with *B. bacilliformis.*

Pathology.—Proliferation of lymphatic endothelium somewhat resembles yaws but more vascular capillary dilatation, and nodules of angioblasts surrounding blood vessels ; Bartonella found in r.b.c. after prolonged search, but confirmation of the identity of Oroya fever and verruga is seen in monkeys with artificially-produced supra-orbital verruga, who develop Oroya fever after splenectomy.

Clinical.—Period of verruga development after Oroya fever : 30–40 days. Initial stages : rheumatic pains and pyrexia as in yaws.

Symptoms subside on appearance of skin lesions. Eruption: sparse, abundant, discrete or confluent; some increase, others abort and drop off; miliary eruption (size of pea): nodular cherry-pink masses. Former more abundant on face and extensor aspect of limbs. Vascular lesions also on mucous surfaces, mouth, œsophagus, stomach, intestine, bladder, uterus and vagina. Dysphagia and hæmatemesis common; melæna; hæmaturia. Nodular eruption chronic with tendency to spontaneous hæmorrhage; dangerous. Mortality nil.

Diagnosis.—Eruption characteristic; may be simulated by yaws, molluscum contagiosum and multiple lipomata. Individual nodules may resemble angioma. Serum agglutinates suspension of *B. bacilliformis* 1 : 10 to 1 : 80. Coagglutination with cultures of *Proteus* OX19, OXK and OX2.

Treatment.—Ulcerated or gangrenous nodules excised. Styptics occasionally required to control hæmorrhage. Chloromycetin (chloramphenicol) as in acute stage (p. 74).

CHAPTER IV

BACTERIAL DISEASES

PLAGUE

Dire fever caused by *Pasteurella pestis.* Normally disease of rat.

GEOGRAPHICAL DISTRIBUTION AND EPIDEMIOLOGY

Almost world-wide. Endemic areas in India, S. China, Uganda, Java. Has occurred in widespread pandemics, as in Great Plague of London. Always present in India—over one million deaths a year, highest in 1907—Madagascar, Mauritius, E. Africa, W. and S. Africa, and to a lesser extent in Brazil, Argentine, S. America, Mexico and (recently) California, South U.S.A. In Ecuador has occurred up to 10,000 ft. Temperature, if very high or low, affects spread. Moderate temperature (50–80° F.) favourable. Seasonal periodicity.

Rat plague follows grain trade, depending on migrations of rat and breeding season of rat flea.

Sylvatic, or wild rodent plague; endemic widespread foci in S. Russia, Kurdistan, Turkey, S. Africa, Manchuria, Central Asia, California, S. America.

ÆTIOLOGY

P. pestis (*Yersina pestis*): Gram-negative, bipolar cocco-bacillus, 1·5–2 μ, with rounded ends and thin capsule. Two well-defined races: (a) glycerol-acidifying, *continental*, in central area of N.W. Asia and (b) glycerol-negative *oceanic* occurring in areas where plague has recently been introduced by sea routes. Three varieties distinguished as *P. pestis orientalis, P. pestis antiqua* and *P. pestis mediævalis.*

Cultivation.—Glycerin-agar, in broth in which butter or coconut oil is dispersed ; forms *stalactite* growth ; no spores.

Experimental.—All laboratory animals susceptible, especially guinea-pig, show œdema round puncture, adjacent lymphadenitis, hæmorrhagic effusions, and death in 24 hours. By cutaneous inoculation die on 3rd or 4th days. Spleen: miliary abscesses with plague bacilli + ; bacilli also in blood.

RAT PLAGUE

In epidemics of human plague (esp. *bubonic*) rat is important starting-point and spread. Principal species : *Rattus decumanus* (grey, Norwegian) and *R. rattus* (black rat) ; mouse, bandicoot rat (*Nesokia*) and musk rat play minor part. Real reservoir of plague infection is a wild rodent in Central India—*Tatera indica*—which has deep and extensive burrows. When it comes into contact with the black rat the infection is passed on to it by the fleas which infest it. In India *R. decumanus* first, then *R. rattus*, attacked, then man. Seasonal prevalence in rats depends on abundance of fleas. Immunity gradually acquired by rat community. In plague epidemic all other animals are affected; dogs immune.

Rats.—*R. decumanus* (*norvegicus*) (sewer rat) : blunt nose, short ears, fine hair on rump, tail shorter than body. Dominant in W. Europe, less so in tropics. Not closely associated with man; burrows under houses, in sewers, etc.

R. rattus (ship rat) : black in Europe, brown in tropics ; pointed nose ; large ears cover eyes when folded ; coarse hairs on rump ; tail longer than body ; climber, arboreal, inhabits roofs, thatch, ships. Dominant and domestic in tropics, in close contact with man.

Rôle of flea.—Plague not communicable by contact. Conveyed by rat flea of tropics (*Xenopsylla cheopis* and, to lesser extent, *X. astia*), dog and cat fleas (*Ctenocephalus canis, C. felis*). Human flea (*Pulex irritans*) is unimportant, but occasionally may carry plague direct from man to man without intervention of rat. In temperate climates fleas are most numerous in summer, hence bubonic plague is disease of summer and autumn. In tropics, temperature above 85° F. is unfavourable, if dry.

Transmission.—In rodent plague, bacilli in blood taken up by flea (1) pass through gut, viable in fæces ; (2) regurgitation—more important. Bacilli shelter in proventriculus, multiply and form solid plug of bacilli so that the flea cannot swallow. When thirsty, flea regurgitates bacilli into wound and bites frequently (" blocked fleas "), due to multiplication of organisms in blood clot in peculiar type of proventriculus.

Fleas (*Siphonaptera*).—Wingless, blood-sucking insects ; eyes and antennæ much reduced ; some have combs on head and thorax. Eggs hatch in summer in 3–4 days. White, hairy larvæ live in dust, feed on débris and fæces of adults. Fully-grown larva spins cocoon, pupates. Resting larval stage in which it can remain dormant for months, also resting stage in adults. *Xenopsylla cheopis* requires higher temperature to develop than other fleas, therefore found in heated buildings in England, America and Russia. Feeds every 10 days. In temperate climates hibernates in adult stage; thereby may remain plague-infected through winter as in rodent-flea plague of Siberia. Antepygidial bristle on short pedestal. Ninth sternite has appearance of a club. In female "tail" of receptaculum seminis is longer than in other species.

X. astia very similar. Male, ninth sternite ribbon-like. In female "head" of receptaculum seminis much wider than "tail." Can carry plague; but not so effectively as *X. cheopis*.

Numerous wild rodent fleas capable of transmitting plague: such are *Oropsylla silantievi* of the giant marmot. In S. Africa numerous rodents, such as the striped and multimammate mouse, have their own species of flea as do the gerbilles. In California the ground squirrels harbour *Ceratophyllus acutus* and *Hoplopsyllus anomalus*.

Flea prophylaxis.—Floors of house washed with solution of naphthalene, benzene, or emulsion of soap and petroleum, diluted with water 1 : 20, made from soft soap and petroleum; 3 pts. of soap melted by heat in 15 pts. of water, 70–100 parts of oil added while hot, shaking and stirring. DDT spray specially adapted to flea destruction.

Cats and dogs in houses should be washed with carbolic soap or strong lather of vermijelli, or powdered with naphthalene or dusted with pyrethrum and DDT.

For irritation of flea-bites apply 1 : 20 carbolic acid.

Cheopis index.—Standard adopted by sanitarians = number of fleas per rat. Less than 1 indicates rat plague will not easily spread; above 1 danger increases; over 5 dangerous; seasonal variations important: general average per annum computed: *i.e.*, number of fleas collected divided by number of rats.

SELVATIC PLAGUE

Pneumonic plague in Mongolia and Siberia associated with giant marmot (*Arctomys bobac*) and susliks (*Citellus*), which hibernate in deep burrows and harbour *P. pestis*; killed for skins. *P. pestis* conveyed by fleas or by aspiration (droplet infection). In Caucasus, pouched marmot (*Spermophilus guttatus*); in Transbaikalia, *S. eversmanni* and *S. dauricus*; also jerboas and gerbilles. In California, ground squirrels; also tree squirrels, marmots and prairie dogs. In S. African high veld, gerbilles, ground squirrels and multimammate mouse. In lower bush, striped mouse and springhaas. In Senegal, a shrew (*Crocidura stampflii*). On Gold Coast, giant rat; Kenya, field rat. In S. America and Argentine "cavies," such as *Microcavia australis* and *Galea musteloides* as well as other rodents, suffer from plague epizoötics.

PATHOLOGY

Subcutaneous ecchymoses and large hæmorrhages. "Buboes," furuncules, pustules, abscesses. Post mortem : engorgement and hæmorrhage into nearly every organ ; congestion and hæmorrhages in spinal cord and brain. Spleen : enlarged, diffluent. Liver : enlarged, focal necroses ; often miliary plague abscesses. Lymphadenitis of all glands, except in pneumonic plague. Lungs : deeply congested, sometimes pneumonic consolidations. Kidneys : inflamed.

CLINICAL FEATURES

Incubation period : 2–15 days. *Prodromal:* anorexia, bone pains. *Invasion:* pyrexia, lassitude, headache, vertigo, rarely rigor. Face has expression of horror. Temperature 103–107° F. Skin dry and burning. Tongue black, dry, furred. Sordes on teeth, lips, nostrils. Low, muttering delirium. Vomiting frequent.

1. **Bubonic (or Zootic).**—75 per cent. show bubo or buboes within few hours to 5th day, usually in groin or axilla (in sylvatic plague especially), rarely in submaxillary, cervical, popliteal, or epitrochlear glands, usually single; vary in size; may be 2½ in.

   General and *constitutional symptoms.*—Enlargement of liver and spleen ; tachycardia ; intermittent pulse ; buboes soften and burst, discharging evil-smelling pus. Indolent sinuses and granulation tissue. Pyæmia may ensue with secondary streptococcal infection. *P. pestis*, at first abundant in pus, may be overgrown by streptococci and other organisms. Contraction and fibrosis cause lymph stasis and œdema. Petechial hæmorrhages—"plague spots." Moist gangrene of skin, or general pustular eruption on hands, feet and pectoral region ("blains"). Death from septicæmia, secondary plague pneumonia, cardiac failure or hæmorrhage.

2. **Septicæmic plague** (*Pestis siderans*).—No lymphadenitis, profound septicæmia, little pyrexia, delirium, subsultus tendinum ; frequently hæmorrhages ; splenomegaly sometimes.

3. **Pneumonic (or demic) plague.**—Formerly considered fatal. Epidemics of 50,000 or more in Manchuria, Siberia, N. China. Originating in marmot-trappers of giant marmot, "tarabagan" (*Arctomys bobac*, in which *P. pestis* may occur as intestinal infection during hibernation). Also in Nigeria, Gold Coast, New Orleans and other localities where plague has occurred in limited epidemics. (Explanation in these cases that starting-point is intestinal hæmorrhage in rats when *P. pestis* is passed in fæces.) Also associated with squirrel plague.

   Myriads of *P. pestis* expectorated in sputum ; inhalation pneumonia ; profuse, watery, blood-tinged sputum. Rigor, headache, malaise, intense prostration, cough, dyspnœa, delirium, stupor, râles, rhonchi. Death on 4th or 5th day. Secondary plague pneumonia may ensue as a terminal phase in bubonic as well as in septicæmic plague.

4. **Meningeal plague.**—Intense meningeal symptoms with pyrexia. May assume chronic form. *P. pestis* isolated from blood.
5. **Pestis minor** (ambulatory plague).—Reported with every considerable outbreak. Mild, febrile symptoms with bubo in groin resembling *lymphogranuloma inguinale. P. pestis* scanty in pus. Recovery after discharge of bubo pus.

Mortality, highest at commencement and height of epidemic, 60–95 per cent. Depends on social condition and hygienic surroundings. Less in bubonic than in other forms.

DIAGNOSIS

Fever and adenitis in epidemic suggest plague. *P. pestis* in blood, gland puncture or sputum. Cocco-bacillus with bipolar staining suspicious. Grows in Haffkine broth with clarified butter (ghee). Inoculate into abdomen of rat, or root of tail of mouse; œdema at site of puncture, hæmorrhagic lymphatic glands, congestion of liver, enlarged dark spleen with miliary-like tubercles and numbers of plague bacilli : death in 48 hours. *P. pestis* to be differentiated from *P. pseudotuberculosis rodentium* by cultural characteristics, by the latter's motility and lack of pathogenicity for rats, also by the production of urease.

Differential diagnosis.—Bubonic from streptococcal infections, lymphogranuloma inguinale, anthrax, filarial adenitis, glandular fever, tularæmia. Pustular from chicken or smallpox. Carbuncular from anthrax. Septicæmic from typhus and subtertian malaria. Pneumonic from other forms of pneumonia, but blood-stained pleural effusion usually present. Secondary plague pneumonia less virulent.

TREATMENT

Since introduction of streptomycin and sulphonamides treatment revolutionized. Chloromycetin and aueromycin now also recommended (Smadel). Morphia best hypnotic. *Buboes:* glycerin and belladonna, fomentations, iodoform dressings. Streptomycin has proved remarkably efficacious *in vitro* and *in vivo*. It acts as well in mice as in men, not only in bubonic, but in septicæmic and pneumonic forms. Action more rapid and effective when combined with sulphonamides such as sulphadiazine or sulphamerazine. Injection of streptomycin 0·125 gm. I.M. at three hour intervals for 72–96 hours (for dosage of other antibiotics see p. 74). Streptomycin, chloromycetin and terramycin all are active in pneumonic plague.

Prophylaxis.—Quarantine based on incubation period of 10 days. Deratization of ships with cyanide method or sulphurous acid (Clayton system), aldrin, dieldrin and other insecticides.

Isolation of plague patients, disinfection of clothing, cremation of dead, burning infected houses, destruction of rats. Guinea-pigs loose in warehouses attract infected rat fleas, showing up source of infection. DDT 0·025 per cent. Warfarin containing *p*-nitrophenol is the most effective rat poison when mixed with oats;

spraying for fleas most efficacious measure introduced in liquid form and in dusts. For larvæ 5 per cent. spray–100 mgm. per sq. foot applied to floor and 3 feet up walls.

In sylvatic plague, California, trapping and poisoning (poisoned grain) of infected squirrels. In S. Africa, gassing gerbille burrows.

Personal prophylaxis.—Isolation of plague cases and contacts. Muslin masks, with goggles, rubber gloves and cotton uniform. There is great danger to attendants and contacts in pneumonic plague.

Prophylactic inoculation.—Haffkine's prophylactic: six-weeks' old culture of *P. pestis* at 30° C. (86° F.) killed by heat + 0·5 per cent. carbolic acid, 4 c.c. (64·9 min.). Injection causes considerable reaction, but gives protection for 20 months.

Otten's avirulent living *P. pestis* injected. Gives minimal reaction. Used on large scale in Java.; similar strain in Madagascar. Results favourable.

MELIOIDOSIS

A glanders-like disease of rodents due to *Pfeifferella whitmori* (also known as *Malleomyces pseudomallei*); accidental in man; resembles tularæmia.

Geographical distribution and epidemiology.—Limited to Burma, Malaya, Singapore, Saigon, Guam, Ceylon, possibly Uganda, also found in Berlin. Beggars, rag-pickers and drug-addicts in Rangoon, Singapore and in hovels in Berlin.

Ætiology.—*Pfeifferella whitmori* resembles *B. mallei:* small bacillus, same size and shape, stained by Leishman; on culture (also like *B. mallei*) liquifies gelatin. Acute orchitis on intraperitoneal injection of guinea-pig (" Strauss reaction "). Laboratory animals easily infected. Characteristic discharge from nose and eyes. *P. whitmori* in urine and fæces.

Reservoir hosts.—Rat, cat, dog, horse. (Intranasal infection.)

Pathology.—Lesions vary considerably. Usually small pulmonary abscesses resembling miliary tuberculosis. Nodules in liver resembling portal pyæmia. *P. whitmori* in blood, urine, fæces. Cutaneous pustules.

Clinical features.—

(A) *Acute.*—Acute diarrhœa and collapse, resembling cholera. Usually high remittent pyrexia. Delirium and mania. Pulmonary lesions resembling T.B.

(B) *Chronic.*—Lesions confined to skin and subcutaneous tissues. Initial sign may be parotitis; common in morphia addicts.

Diagnosis.—By isolation of *P. whitmori* from urine, fæces and blood; also from C.S.F. Serum agglutination +, 1 : 2,500–1 : 3,000.

Differentiation from *B. mallei*: patients with *P. whitmori* give + test to *mallein*, while horses with melioidosis give negative. Central infiltration with slight tendency to extension characterize melioidosis reaction by subcutaneous injection of *mallein*. May be difficult to distinguish from achromogenic forms of *Ps. pyocyanea.*

Differential diagnosis.—From glanders, tuberculosis, malaria, typhoid, plague, cholera and liver abscess.

Treatment.—Most die in 10 days. Chronic cases are ill for 8 months or longer. Chloromycetin now said to be specific.

TULARÆMIA

An infectious disease of rodents, caused by *Brucella tularensis*, transmitted to man by biting flies, resembling plague.

GEOGRAPHICAL DISTRIBUTION AND EPIDEMIOLOGY

Originally discovered in ground squirrels in California and now widely spread in U.S.A., Scandinavia, Germany, Austria, Russia, and Japan. Mostly in butchers, handlers of skins, trappers and hunters. In U.S.A. and Russia, prevalent June to August ; in Scandinavia, July to October.

ÆTIOLOGY

Br. tularensis : small, 0·3–0·7 μ, Gram-negative, stains best with Giemsa. Cultures on serum-glucose-cystine agar, best obtained by inoculation of mice and guinea-pigs. Occurs in enormous masses in spleen. Originally classed as *Pasteurella*, now allied to *Brucella* group; cross-agglutination with *Br. melitensis* and *abortus*. Pathogenic for most laboratory animals and squirrels.

Transmission.—By gad-fly (*Chrysops discalis*, see p. 227) in Western U.S.A. ; also by stable fly (*Stomoxys calcitrans*), bed bug, squirrel flea, rabbit and mouse lice, ticks (*Dermacentor andersoni*, *D. variabilis* and the rabbit tick). In Sweden, by mosquito (*Aëdes cinereus*).

Reservoir hosts.—Natural infection in wild rodents. In U.S.A., cotton-tail, jack, and snowshoe rabbits, ground squirrel, meadow mouse, possibly beaver, also grouse, quail and horned owl. In Europe and Asia, hare, rabbit, muskrat, water-rat, field vole. In Norway, the lemming (lemming fever).

PATHOLOGY

Rarely fatal in man. Human pathology unknown. Inoculated guinea-pigs' appearances rather resemble plague. Spleen : diffusely enlarged, necrotic foci with *Br. tularensis*, stained by Twort's light-green and neutral-red.

CLINICAL FEATURES

Incubation period 1–10 days.

1. **Local.**—Papule at site of inoculation, with secondary lymphangitis. May be initial ulcer ; nodules in lymphatics may resemble sporotrichosis and may suppurate. Lymphadenitis of groin and axilla.

2. **Generalized.**—Fever, headache, lassitude +, pyrexia, epistaxis. Temperature, 104° F. for 3 weeks. Sometimes roseolar, nodular and pustular rashes. Debility persists for months. Spleen not palpable.
3. **Ocular.**—Parinaud's conjunctivitis. Ocular-glandular infection with *Br. tularensis* through conjunctiva. Chemosis; enlargement of pre-auricular lymphatic glands.

Immunity.—Lasting, but local reinfection may occur. N.B.—Dangerous organism in laboratory. Laboratory infections frequent.

DIAGNOSIS

Inoculation of biopsy material into guinea-pigs, mice and rabbits. *Br. tularensis* rarely found in blood. Serum agglutinates emulsions of organism in high dilutions (also co-agglutination with other members of Brucella group). Emulsions made from spleens of infected mice.

Intradermal test, with killed cultures, fairly reliable.

Differential diagnosis.—From other forms of lymphangitis, especially plague.

TREATMENT

Bed for 3 weeks after subsidence of fever. General lines.

Antiserum (Foshay, 1940), serum from goats injected with *Br. tularensis*, 10–25 c.c., intravenously or intramuscularly to children, 50 c.c. to adults. **Streptomycin** more specific for this than for any other disease. I.M. injections 1 gm. daily for 7 days. Chloromycetin also effective.

Prophylaxis.—Avoidance of contact with infected rodents. Rubber gloves worn in skinning rabbits. Care in laboratory essential. Cooking and freezing meat destroys infection. Spray dead rodents with DDT.

UNDULANT FEVERS (BRUCELLOSIS)

Term "undulant" originally applied to fever of Malta and Mediterranean. Now world-wide; organism known as *Brucella* was originally considered to be a *Micrococcus*. The following are now recognized :—

1. *Brucella melitensis*, organism peculiar to goat ; conveyed to man in goat's milk. Serological variety in Algiers, *Br. paramelitensis*, possibly connected with sheep's milk. More or less tropical and subtropical distribution.
2. *Brucella abortus* (formerly *Bacillus abortus*, Bang), produces epidemic abortion in cow. A variety occurs in pig (*Br. suis*), especially in U.S.A. Found all over the world, wherever epidemic abortion of cows occurs.

A.—UNDULANT FEVER (MELITENSIS TYPE):

Malta or Mediterranean fever

GEOGRAPHICAL DISTRIBUTION AND EPIDEMIOLOGY

More widely distributed than formerly thought. Not confined to Malta or even Mediterranean. Italy, France, Spain, Red Sea provinces, India (Punjab), China, S. Africa, Somaliland, W. Africa, West Indies, S. America, and South U.S.A., especially Texas, Mexico, Philippines. Extremely difficult to define exact range owing to close resemblance between *melitensis* and *abortus*. Since 1945 found in Pfalz region of Germany in goats and sheep and in shepherds.

Most susceptible age : 6–30 years. In Malta, indigenous inhabitants suffer as do immigrants. May assume epidemic character. Greatest prevalence : season of lowest rainfall—June–September—reverse of typhoid.

Explanation : greater use of goat's milk in summer months. Contamination of milk more marked after birth of kid. Occurs in particular towns, villages, barracks; ship epidemics formerly reported when transporting Maltese goats. Disease has disappeared in naval and military forces in Malta, but still prevails in civilian population.

Transmission.—Usually conveyed by milk, especially goat's milk, in Malta and Gibraltar. *Br. melitensis* in 10–50 per cent. of goats. Undulant fever ceased in naval and military hospital on prohibition of goat's milk. Goat's milk cheese also infective. Infection also possibly conveyed by manure and in dust (*Br. melitensis* passed in goat's urine). Water-borne outbreak recorded in Michigan, U.S.A. (1938).

ÆTIOLOGY

Br. melitensis recovered by cultivation from spleen pulp and lymphatic glands. Monkeys susceptible ; easily infected by feeding.

Br. paramelitensis : Tunis, Algeria, probably serological strain.

Br. melitensis : 0·33 μ in diameter, usually single, sometimes in pairs. Gram-negative ; cultivated in alkaline-agar (pH 6·8–7·4), special beef or liver media (Staffseth's medium) at 37° C. (98·6° F.) grows slowly ; small, round colonies 2–3 mm. Cultured from blood and urine (10 per cent.) of man, also in milk and urine of Maltese goats (50 per cent.) ; probably occasionally in cows. Morphologically identical with *Br. abortus;* separable by absorption tests. Serum from *Br. melitensis* cases also agglutinates *Br. abortus;* latter less pathogenic for monkeys.

N.B.—Laboratory infections frequent. Care in handling cultures. Nurses and doctors can contract disease direct from patient.

PATHOLOGY

Spleen enlarged (17 ozs. : 52·8 gm.) ; soft, diffluent ; congestion and sometimes ulceration of intestinal mucosa. Toxic damage to other organs. Sometimes flattening of cortical convolution of brain, and effusion into ventricles.

CLINICAL FEATURES

Incubation period uncertain ; may be 6 days, but may remain latent for months. Initial stage : lassitude, headache, bone pains, post-ocular pain on lateral movement ; pain in temporo-mandibular joint ; sometimes diarrhœa. White fur on dorsum of tongue ; congested pharynx ; anorexia ; epigastric tenderness. Pulmonary congestion. Delirium occasionally, usually insomnia. Pyrexia remittent ; temperature rises midday and after (2–4 p.m.). Profuse sweats ; then enlargement of liver and spleen. Primary span of fever from 3 weeks to 3 months. Intense lumbar pain. Fleeting rheumatic pains in joints and fasciæ ; skin hot and tender ; no effusion. Pressure points especially painful—sacro-iliac joint, heels, wings of scapulæ ; supra-orbital and intercostal neuralgia. Orchitis and epistaxis occasionally. Blood changes few ; in prolonged cases slight secondary anæmia ; usually slight reduction in leucocytes (6,400) with rise of lymphocytes and reduction of polymorphonuclears.

Gradual defervescence, with improvement of symptoms, succeeded by another febrile bout and so on. Undulating fever with ladder-like rises to 103 or 104° F. (39·5–40° C.). Relapses recur for 3–9 months, occasionally last a year or longer (average 4 months).

Continued type.—High remittent pyrexia without sweats or joint pains ; rare.

Intermittent type.—Marked daily excursions not uncommon. Sometimes mild rigors ; may resemble sepsis, tuberculosis, endocarditis. All degrees of severity ; ambulant, mild, acute, malignant, intermittent.

Malignant type.—Hyperpyrexia and toxæmia. Death after one month's duration reported from Sudan.

Meningeal type.—Rare ; increased pressure of C.S.F.

Rarer types.—Hydrarthrosis of one or more joints without general disturbance, occasionally.

Surgical.—Localized deep abscess on chest wall, or elsewhere. Chronic osteomyelitis of tibia rare. (*Br. melitensis* isolated from pus.)

Complications and sequelæ.—Emaciation, anæmia, persistent rheumatic pains, especially in sacro-iliac joint. Occasionally chronic arthritis, sciatica, mastitis, parotitis, ovarian pain, dysmenorrhœa, amenorrhœa (usually), sometimes menorrhagia. Abortion in pregnant women. Intermittent hæmorrhages from urethra (inflammation of seminal vesicles). Infection of fœtus recorded. Gastric and intestinal hæmorrhage may cause death, also hyperpyrexia. Secondary complications : tuberculosis or pneumonia.

DIAGNOSIS

Character of fever and general symptoms.

Blood culture.—5 c.c. blood, well diluted in nutrient broth (blood clot preferable), incubated for 5 days ; occasionally positive on 23rd day ; positive *throughout course of fever.* Also obtained by splenic puncture.

Urine culture.—From second week; 5 c.c. of urine (midstream or catheter). Strict aseptic precautions necessary.

Agglutination.—Serum heated to 56° C. (132·8° F.) for half an hour (non-specific agglutinins). Zone of pro-agglutination (zone of no reaction in low dilutions) sometimes.

Macroscopic test (better), dense emulsion of organism, snow-flake agglutination, rocking slide test preferable. (Serum of tularæmia may agglutinate *Br. melitensis.*) Agglutinations below 1 : 50 should not be regarded as diagnostic. Rising titre of agglutination more important than absolute titre.

Intradermal " melitene " reaction.—0·2 c.c. of killed broth culture of *Br. melitensis* (500,000 organisms) injected intradermally: œdematous hyperæmic zone (4–6 cm.) with outrunners visible for several days (+ in 6 hours). Control test with broth and other organisms advisable. Weak positive reactions merely indicate sensitization, not necessarily infection.

N.B.—Should not be repeated as abscess or skin gangrene may ensue.

Animal inoculation.—Guinea-pig, very susceptible.

Differential diagnosis.—Especially from typhoid by character of fever, rapid pulse, sweats, absence of rash. From tuberculosis, empyema, chronic malaria, relapsing fever, endocarditis, liver abscess.

Mortality.—2–6 per cent.; malignant type 10 per cent. Continued temperature 104° F. (40° C.) unfavourable.

TREATMENT

General nursing in blanket. Liberal diet. Hydrotherapy, continuous sponging with tepid water. Frequent changing of bed clothes.

Aureomycin. terramycin, chloromycetin and other antibiotics cause defervescence of fever and in many cases a cure. Alternation of two former advisable in resistant cases. A total daily dosage of 3 mgm. per kg. (about 0·2 gm.) 6 hourly is well tolerated. Large amounts may have to be given, up to a total of 36 gm.

Prophylaxis.—In endemic areas milk to be avoided, unless sterilized by boiling, also sheep's and goat's milk cheese. Destroy infected goats; *Br. melitensis* cultivated from blood or milk. *Lacto-reaction*: dilute goat's milk 1 : 200, mix with dense emulsion of *Br. melitensis*—agglutination produced.

Prophylactic inoculation.—3 injections of 500–2,000 million killed organisms.

B.—ABORTUS TYPE

Milder disease on the whole. *Bacillus abortus* (Bang) recognized since 1918 as closely related to *Br. melitensis*.

GEOGRAPHICAL DISTRIBUTION AND EPIDEMIOLOGY

World wide: England, Denmark, Sweden, Germany, Holland, Switzerland, Austria, Poland, Palestine, S. Africa, Rhodesia, Australia, New Zealand, U.S.A. (apparently widespread there, especially in Michigan). Conveyed in cow's milk ; sporadic, but common in cowmen, shepherds, veterinary surgeons, farmers. Porcine type in slaughter houses, meat packers, Chicago and S. France.

ÆTIOLOGY

Br. abortus from blood, urine and fæces of patients, closely allied to *Br. melitensis*.

Varieties : (a) *Br. abortus bovis*—cow, from 6·3 per cent. of cow's milk.
(b) *Br. abortus suis*—pig, in pig carcases in U.S.A. and England.
(c) *Br. abortus equi*—? horse.

Differentiation.—*Br. abortus* little larger than *Br. melitensis*, pleomorphic. *Grows best under* 10 *per cent. carbon-dioxide tension.* Requirements for this diminish on subculture. On potato slopes alkaline reaction gives creamy-yellow growth (*Br. melitensis* and *paramelitensis* brownish or blackish).

Reaction to dyes.—*Br. abortus bovis* inhibited by thionin.
Br. abortus suis „ „ basic fuchsin, methyl violet, pyronin.
Br. melitensis grows in presence of all four dyes.

H_2S production from proteins, or amino-acids grown on Staffseth's liver-infusion agar at *p*H 6·6. Blackening of lead acetate paper shows presence of free lead.

	Carbon dioxide requirement	H_2S *production*	*Inhibition of Growth by Thionin*	*by basic fuchsin*
Br. melitensis	—	—	—	—
Br. abortus bovis	+	+	Inhibition	—
Br. abortus suis	—	++	—	Inhibition

Culture.—From milk by cultural method, seeded with liver extract ; peptone-agar with 1 : 10,000 gentian violet in 10 per cent. CO_2 atmosphere, or by injecting 0·5 c.c. subcutaneously into guinea-pig, killed after 3–4 weeks. Enlargement of spleen ; inguinal and lumbar glands contain organisms ; tubercle-like foci. Culture from blood or spleen in man comparatively easy ; more difficult from urine and fæces.

Br. bovis in cattle. Inflammation of uterine mucosa and vaginal discharges. Lymphatic spread in udder and teats and in lymphatic glands. Also infects genital passages of bull. Occurs in epidemic form ; later chronic and endemic. Pregnant cow infected ; abortion 8–10 days later: in chronic type 5–7 months.

PATHOLOGY

Same as in *Br. melitensis* fever as far as is known. Occasionally abscesses of spleen. Reticulo-endothelial hyperplasia of lymph glands. Meningo-encephalitis with greyish-white tubercles in *Br. suis* infections in U.S.A.

DIAGNOSIS

Cultivation of *Br. abortus* from milk and inoculation into guinea-pig.

Macroscopic agglutination (" abortoscope "), 1 : 10,000 dilution with whole blood.

Intradermal test (" abortin reaction "), infiltration and œdema ; used by veterinarians. Diagnosis in man as for melitensis type.

Agglutination reaction in low dilutions, 1 : 10–1 : 80, not diagnostic (? due to absorption of agglutinins in cow's milk).

Blood culture.—Precautions as above for *Br. melitensis*. Blood shows slight leucopenia, relative lymphocytosis.

CLINICAL FEATURES

Same as in *Br. melitensis* type ; usually milder. Short, symptomless fevers common. May become exceedingly chronic. Laboratory infections particularly severe. Six types :—(1) Mild, (2) Classical undulant, (3) Abdominal, (4) Genital-orchitic, (5) Arthritic, (6) Catarrhal jaundice type. Spleen usually not enlarged. Sometimes orchitis and lymphadenitis are sole features. Hæmorrhages in severe forms : epistaxis, hæmoptysis, hæmatemesis, hæmaturia, menorrhagia, bleeding of gums, purpura, jaundice. Localized " *brucellosis* " : abscesses in muscles; occasionally osteomyelitis. Rarefying osteitis of metatarsals rare. Meningo-encephalitis reported in U.S.A. Mild cases with temperature 99–100° F. (37·5–38° C.); headache the only symptom.

TREATMENT

Aureomycin and other antibiotics effective as in *Br. melitensis*, by same method and same dosage. Also favourable results reported in *Br. suis* infections. Some strains of *Br. abortus* are sensitive to streptomycin, especially when combined with sulphadiazine. In S. Rhodesia antrypol has been given intravenously in combination with above.

Prophylaxis.—In dairy herds : detection of sick animals and carriers. Control of all milk supply necessary, but probably impracticable. Only solution is universal pasteurization of milk—30 mins. at 140–150° F. (60–63° C.). Problem more difficult in meat packers. Prophylactic inoculation not yet inaugurated.

BACILLARY DYSENTERIES

Acute epidemic diseases ; infection of mucosa of large intestine by specific dysentery bacilli. Often attended by high mortality.

GEOGRAPHICAL DISTRIBUTION AND EPIDEMIOLOGY

World-wide, not confined to tropics, but generally more severe there. Certain types found in Europe, England and U.S.A. In tropics : epidemics in crowded communities, prison camps, barracks, schools, bazaars, and workers on tea and rubber plantations. Nearly always present in lunatic asylums. Important war disease in 1914–18; virulent epidemic in Gallipoli, 1915, also in France. During second World War in Poland, Russia, Near East, Palestine. Specially virulent in children.

Spread.—Direct contagion from *fæces* under primitive sanitary conditions and in lunatic asylums from carriers.

Flies.—Housefly vector of infection; feeds on dysenteric fæces and vomits on to food, also passes bacilli in dejecta.

Water.—Medium of infection in Malaya; dysentery bacilli can survive in water 3 weeks.

Milk.—Outbreaks of Flexner and Sonne dysentery in England ascribed to contamination of milk.

Food.—Sonne dysentery particularly a food infection in meat and vegetable puddings.

Susceptibility of individual.—Immunity to infection probably produced by long residence and repeated infection. New arrivals in tropics more liable than old residents. Bacillary dysenteries are frequently terminal infections in other debilitating diseases, such as malaria and tuberculosis.

Definite seasonal incidence.—In Middle East vernal and autumnal outbreak, possibly associated with prevalence of flies; in tropics, disease of rainy season. Also connected with flies, waterlogging of soil, crowding together of natives in huts, increasing chances of infection and risk of pollution of water.

ÆTIOLOGY

Shiga's bacillus (*Shigella shigæ*): characteristic virulent dysentery bacillus; rod-shaped, Gram-negative, 1–3 μ by 0·4 μ, non-motile, but active Brownian movements. Produces acid in milk, acid from glucose, no indol; agglutinated by specific serum and by serum of infected patients. Produces exotoxin. More frequent in tropics, causes most severe forms of disease and greatest number of deaths and complications.

Schmitz's bacillus resembles above, but produces indol; agglutinated by specific serum.

Flexner's bacillus (Flexner group) resembles Shiga, but less toxic; produces acid from mannite and, in peptone water, indol, with exception of Newcastle bacillus which ferments dulcite. Has six different strains and antigenic components (Boyd, 1938); specific antigen disappears on subculture leaving group antigen. Now type-specific suspension used for agglutination and other tests. Pooled strains.

Newcastle bacillus now held responsible for many mild outbreaks of dysentery, especially in children in Europe, as well as in tropics. Differs from other dysentery bacilli in sometimes producing gas in the sugars.

Sonne's bacillus is extremely common—especially in children—in epidemic form in temperate zones, and also cause of acute diarrhœa in tropics. Ferments lactose, saccharose and glucose. Agglutinated by specific serum. Colonies crenated ; with lactose media : red central point.

PATHOLOGY

Inflammation and toxic necrosis of mucosa of large intestine (coagulation necrosis). Usually most intense in rectum and sigmoid, but lower third of ileum also affected. Gut contracted to narrow, rigid tube ; mucous membrane olive-green, brown or black and bile-stained. Often irregular in distribution, alternating with areas of normal mucosa. Lymphoid peritonitis often. Toxic damage to liver and other organs. Toxæmic nephritis. In chronic form ulceration of mucous membrane, sinuous submucous tracks in rugose mucosa resembling "cobble stones." Submucous retention cysts. Granulation tissue formation, leading to partial or generalized stenosis.

Microscopic pathology.—Submucosal hæmorrhages ; round-cell infiltration ; endothelial proliferation of histiocytes ; plasma cells apt in sections to be mistaken for *Entamœba histolytica*.

CLINICAL FEATURES

Incubation period : 1–7 days. Onset : insidious or sudden ; all degrees of severity. Main symptoms referable to inflammation of large intestine ; colic, tenesmus, blood-stained mucous fæces. Usually pyrexia, but in most severe cases often none. Tenesmus very distressing. Dysuria frequent in severe cases, vomiting common. Abdomen sunken, navicular ; superficial and deep abdominal tenderness ; spastic contraction of large intestine, especially sigmoid.

Stools.—Diarrhœa at first, then blood and mucus +, stools small in amount, uncountable in number with pain and straining; viscid and gelatinous ones resemble red-currant jelly (to be distinguished from amœbic stool, p. 46) ; later exudate becomes more purulent ; finally, in 3rd to 4th week, fæcal. In most acute and fulminating cases the large proportion of dark blood causes them to resemble "meat washings."

MILD FORM.—Diarrhœa, watery stools, gradually becoming more mucoid, with urgency and griping ; lasts 1–2 days ; no pyrexia ; usually Flexner or Sonne infection.

ACUTE FORM.—Onset abrupt ; stools, blood-stained mucus, + griping, tenesmus, dysuria. Pyrexia ; sometimes rigor. Signs of general toxæmia ; malar flush ; anorexia, furred tongue, rapid pulse. Navicular abdomen ; rapid emaciation. Attack lasts 2–3 weeks. Usually Shiga infection.

FULMINATING FORM.—Acute and sudden, often with rigor. Toxæmia from commencement. Toxic cyanosis ; low blood pressure ; peripheral vascular failure. Vomiting, initial pyrexia, subsequently subnormal. Stools uncountable ; much dark blood ; "mousy" odour. Abdomen, at first sunken and acutely tender, becomes insensitive. Often uncontrollable hiccough. Death from toxæmia.

CHOLERAIC FORM.—Profuse, colourless stools ; resembles cholera.

RELAPSING FORM.—In certain proportion of subacute cases relapses occur with blood and mucus in stools.

CHRONIC FORM.—After initial subacute attack, chronic diarrhœa, occasional blood and mucus, emaciation +, secondary anæmia. In natives associated with other infections (ancylostomiasis and malaria) ; produces " walking skeletons."

BACILLARY DYSENTERY IN CHILDREN.—Acute and rapidly fatal from toxæmia; may be ushered in by convulsions; accompanying pyrexia may suggest " enterica."

Flexner dysentery.—Impossible to differentiate on the whole from Shiga dysentery ; generally much milder and complications less severe. Newcastle bacillus dysentery resembles foregoing.

Schmitz dysentery.—Resembles Shiga dysentery.

Sonne dysentery.—Frequent in England. May produce typical Flexner-like dysentery ; pyrexia and toxæmia. Fæces greenish or " tomato soup." Pyrexia and acute onset common ; continued pyrexia and vomiting resemble other forms of food poisoning. Catarrh of respiratory tract, bronchitis and rhinitis, frequently associated. Sonne bacilli numerous in fæces, easily isolated. Occasionally may cause sudden death in children.

Causes predisposing to bacillary dysenteries.—Physical exertion, unsuitable dietary, exposure, malaria, tuberculosis, scurvy, enteric.

Complications.

Dysenteric arthritis (dysenteric rheumatism) frequent in some epidemics (Shiga infections) : synovial effusion into joint cavity and tendon sheaths, also periarticular with pyrexia and rigor may ensue in acute stage, with blood and mucous stools ; more usually during convalescence, after 20th day ; occasionally all joints affected, including interphalangeal and temporo-mandibular ; resembles acute rheumatoid arthritis. May persist 6 weeks or longer ; rarely causes permanent disability or deformity. Differentiation from gonorrhœal arthritis by aspirating synovial fluid, which is sterile and agglutinates dysentery bacilli in high dilution. Arthritis not reported in Sonne infections. Peritonitis with serous effusions rare. Toxæmic nephritis with albumin and casts in urine and nitrogen retention.

Parotitis and intussusception of small intestine common in children.

Perforation of colon rare ; sometimes chronic peritonitis with effusion.

Eye complications.—Toxic conjunctivitis in acute stage. Iridocyclitis often with arthritis. Irregular pupils ; anterior uveitis ; photophobia; blepharospasm. Aqueous humour may agglutinate Shiga bacillus.

Sequelæ.—Stenosis of bowel and adhesions ; rarely megacolon. Mucous colitis. Peripheral neuritis occasionally ; post-dysenteric tachycardia; achlorhydric dyspepsia. *Reiter's disease*—a combination of non-specific urethritis, conjunctivitis and arthritis with fever, malaise and raised E.S.R.—may be independent condition or sequel. Arthritis affects larger joints of lower limbs with effusions and circumscribed areas of tenderness over the periosteum. Skin rashes and general lymphadenitis are common. There may be recurrences.

Carrier state.—Dysentery carrier = *convalescent carrier.* Incomplete recovery, with blood and mucus in fæces. Healthy carrier, as in typhoid, very rare. Dysentery bacilli persist in submucous retention cysts. Carrier state usually persists 4–6 months; maximum about 3 years. With improved methods of cultivation (anal swab method) and selective media, more carriers recognized than formerly; 3–10 per cent. in recovered cases. In Sonne dysentery more frequent (20 per cent.). Rarely, granular rectitis persists, with blood and mucus passed after defæcation containing bacilli.

DIAGNOSIS

Differentiation from amœbic dysentery most important. Apyrexial mild forms without clinical signs may be difficult in absence of laboratory investigations; subtertian malaria or other forms may complicate bacillary dysenteries. Character of stools helpful; microscopic examination of cellular exudate (cytodiagnosis), polymorphonuclear leucocytes with ring nuclei, macrophage cells (histiocytes) from proliferated capillary endothelium contain ingested r.b.c. and other débris; refractile, globular or irregular; *apt to be mistaken for E. histolytica. E. coli*, other amœbæ, *Giardia* and the flagellate protozoa may all be found in dysenteric exudates.

By culture.—Blood and mucus from stool spread on special media (MacConkey, Conradi-Drigalski, desoxycholate agar): recognition of typical round dew-drop like colonies of dysentery bacilli. *Specimen must be freshly passed* and free from urine contamination. Specimens despatched in tropics should be packed with ice, or emulsified with 30 per cent. glycerine in 0·6 per cent. saline, or by adding equal volume of $\frac{N}{33}$ NaOH solution, rendering them alkaline; packed in wide-mouthed screw-capped, grease-proof cardboard tumbler. Rectal swabs dipped in saline agar n tumbler assure viability of organisms which, by this method, remain alive for several days at 15° C. Identify colonies by emulsion and macroscopic agglutination with specific serum. Subcultures inoculated into solution of sugars—glucose, mannite, saccharose, dulcite. Bacilli recovered from intestinal mucosa *post mortem*—not from bile or organs—occasionally from mesenteric glands and blood.

Recent experience indicates that best method is combination of fæcal culture with rectal swabs (through proctoscope), especially in Sonne infections. Selective media: Liefson's desoxycholate-citrate medium. Superior to MacConkey for Flexner and Sonne.

Serological diagnosis.—Of little practical value. Agglutinins absent in acute cases and often not present till convalescence. Most reliable in Shiga cases; Shiga positive 1 : 25 and over diagnostic; Flexner 1 : 100 and over diagnostic. More often useful in chronic cases.

Dysenteric agglutinins present in cellular exudate in fæces. Leucocytosis (16,000–30,000) at commencement of attack, rapidly falling to normal on third or fourth day.

Sigmoidoscopy.—In acute stages: necrosis of mucosa. In chronic: granular, velvety mucosa, easily traumatized. Bleeding ++. Rigid infiltrated and stenosed lumen. Ulceration seldom seen. Instrumentation painful. In chronic stage, differentiation from ulcerative colitis difficult.

TABLE V

Differential Diagnosis of Bacillary from Amœbic Dysentery

Bacillary Dysenteries	*Amœbic Dysentery*
Acute disease—"lying down dysentery."	Chronic—"walking dysentery."
Incubation period short.	Incubation period long.
Acute onset with pyrexia.	Onset insidious, usually apyrexial.
Limited disease (2–3 weeks).	Prolonged course.
Superficial and deep abdominal tenderness; tenesmus +.	Localized deep tenderness; tenesmus rare.
Stools—scanty, numerous, bright red, viscid mucus, odourless. "Red-currant jelly."	*Stools*—+ blood and mucus, very offensive, less numerous, larger in amount. "Anchovy sauce."
Reaction alkaline.	Reaction acid.
Numerous pus and macrophage cells.	R.b.c. in rouleaux. Macrophage cells scarce or absent; few pus cells. Charcot-Leyden crystals. Active *E. histolytica.*
Blood—preliminary leucocytosis.	*Blood*—persistent slight leucocytosis.
Sigmoidoscopy—granulation tissue and inflammatory changes in mucosa.	*Sigmoidoscopy*—amœbic ulcers in rectum, and "pigskin pittings."

Prognosis.—In well-nourished Europeans usually good. Mortality rate seldom above 5 per cent. In ill-nourished natives may be 40–50 per cent. Prognosis bad, if complicated with other disease—*e.g.*, malaria, which in bacillary dysentery may be terminal infection.

TREATMENT

Nursing in bed essential. Preliminary treatment as for shock. Tinct. opii, or morphia, for pain. Blood or plasma transfusion beneficial. In dehydrated cases intravenous injection of glucose (5 per cent.), saline and adrenaline. In fulminating dysentery with continuous stools patient should be nursed on mackintosh sheet and packed with tow. Bedpan may cause undue distress and straining.

Diet.—Fluids +: meat jellies (Brand's essence), albumin water, rice water, arrowroot, sago; milk not recommended. Two-hourly small feeds. Moro's apple diet recommended in recent war; apple pulp, up to 2 lbs. daily, and lemon juice (for vitamin C).

Saline treatment.—Saline aperients. Sodi sulph., ʒ i with water, every four hours till stools become fæculent. Some prefer *pulv. rhei co.*

Anti-dysenteric serum.—Modern concentrated anti-Shiga serum injected intravenously, 5–10 c.c., in toxic Shiga cases. Recent experience in favour of combining with sulphaguanidine.

Sulphonamides—*Sulphaguanidine* in Shiga and Flexner infections. Initial dose: 0·1 gm. per kilo.; subsequently 0·05 gm. per kilo. every 8 hours for 3 days. In Middle East 10–20 gm. (54–308 gr.) daily for 5 days or longer with benefit; aggregate 135 gm. for each case. Mild and acute Shiga infection 20 gm. daily for 2 days; 10 gm. for 3 days. Kills dysentery bacilli in lumen of gut. Stools become fæculent in 5 days. Absorbed by blood in minimal amounts (1 mgm. per cent.). Therefore toxic phenomena not observed: no agranulocytosis; occasional purpuric rash. Less efficacious in Sonne. Cures carrier state. If constipated, aperients necessary. Recommended in chronic stage; then may be continued for 12 days or longer. Healing of bowel observed by sigmoidoscopy. In chronic resistant forms better result obtained by sulphaguanidine retention enemata (5–7 gm.: 77–107 gr.) suspended with mucilage in 7 ozs. (296·5 c.c.) water. Other sulphonamides, sulphadiazine, sulphamezathine and phthalyl sulphathiazole. The latter recommended for Sonne. Dose 10 gm. daily for one week. Succinylsulphathiazole 4 gm. daily for same period. All should be given with plenty of water; possibly are less toxic than sulphaguanidine. Streptomycin by mouth is poorly absorbed, though combined treatment with sulphonamide very effective. Local strains of dysentery bacilli should be tested for sensitivity. Dose of streptomycin up to 4 years should be 1 gm, 4–12, 2 gm. and for ages above, 4 gm. in four daily doses for five days. 1 gm. streptomycin dissolves in 1 dr. (3·5 c.c.) of water. Sonne bacillus is more sensitive to streptomycin and this is combined with sulphaguanidine in a preparation—guanimycin.

(**Bacteriophage** treatment much used in India, Egypt and elsewhere. Results questionable.)

Treatment of complications.—Iritis and arthritis: on general lines; sulphaguanidine beneficial. In desperate cases of chronic form: appendicostomy, ileostomy or cæcostomy used to be performed; probably no longer necessary.

Prophylaxis.—General sanitation; protection of food from flies Elimination of carriers. Sulphaguanidine treatment now efficacious, especially in Sonne carriers and when combined with saline aperients.

CHOLERA

A very severe infectious epidemic disease with a high mortality.

GEOGRAPHICAL DISTRIBUTION AND EPIDEMIOLOGY

Endemic in Bengal; thence epidemics spread over India. Has occurred in pandemics all over Europe; last in Hamburg in 1892. Has spread to West Indies and U.S. ; now prevalent in India, China, Iraq ; favoured by pilgrimages—Hurdwar and Mecca. Follows main routes and is spread by man from place to place. Isolated countries—Andaman Islands, Australia, New Zealand, Pacific Islands, Cape Province and West Africa—have escaped.

Endemic foci in India and Burma related to water system near coast and at low level, but it has not been possible to trace the manner in which infection is maintained or method of infection from patient to patient, especially in the inter-epidemic periods.

Water-borne infection ; most severe when water supply as a whole is infected. In Eastern countries, confined to cisterns and wells. Absolute humidity of 0·400 necessary. Rise and fall of cholera ascribed to production of special bacteriophage (choleraphage).

ÆTIOLOGY

Cholera bacillus, *Vibrio choleræ*, usually known as " comma bacillus " 1·5–2 μ by 0·5 μ, half length and twice thickness of tubercle bacillus ; long flagellum at each end confers active spirillum-like movements. Stained best by watery solution of fuchsin ; Gram-negative.

Cultivation in alkaline medium, broth, blood serum, agar, gelatin, potato ; characteristic surrounding liquefaction in gelatin stab-culture. In alkaline peptone water, forms film on surface. Does not hæmolyse blood agar. Cholera-red reaction : addition of H_2SO_4 to culture in 1 per cent. peptone water. Many other vibrios resemble *V. choleræ* ; differentiation sometimes difficult. With specific immune rabbit serum agglutinated to titre 1 : 12,000.

Disease difficult to reproduce in experimental animals and also in man. Bacteriological proof : non-hæmolytic vibrio with specific O antigen. Toxin (endotoxin) produced by disintegration of vibrios.

Multiplies in small intestine, where endotoxin is liberated.

Tranmission.—Infection conveyed by water, food or soiled clothing. Milk, raw fruit, vegetable and uncooked foods act as media. In fæces, in absence of light, *V. choleræ* survives 8 days ; when dried, dies in few hours; in reservoir water, lives 2 weeks. Clam, *Meretrix casta*, found in river estuaries in E. Coast of India, is used as food. Fishermen liable to cholera. No evidence that multiplication of vibrios takes place inside these shellfish.

Cholera carriers common. May be as high as 20 per cent. in contacts. 6 per cent. of healthy contacts excrete vibrio for 2 months.

Immunity.—Pfeiffer's reaction : culture of *V. choleræ* added to 1 c.c. of broth containing 0·001 c.c. of anti-cholera serum ; injected into peritoneal cavity of guinea-pig and examined by means of capillary tubes every few minutes; true *V. choleræ* break up rapidly.

PATHOLOGY

Rigor mortis early. Contractions, dehydration of tissues and rupture of muscles. Dilated right auricle with imperfectly coagulated blood. Liver congested; gall-bladder distended with bile. Surface of bowel rosy-red ; lumen containing rice-water material and large numbers of vibrios. Gall-bladder and bile canaliculi invaded by *V. choleræ* which can also be isolated from blood, kidneys and spleen and may be present in urine. The kidneys show patchy ischæmia of cortex or medullary congestion and there may be necrosis of urinary tubules. It is thought that vasospasm is responsible for cessation of urinary secretion, but probably not for tissue changes. Suprarenal glands show depletion of lipoids from the cortex which may be associated with liberation of cortical hormones.

CLINICAL FEATURES

Incubation period : short, probably a few hours ; average 3–6 days. Onset : sudden, or supervening in course of mild premonitory diarrhœa. Profuse watery stools soon become rice-water, containing mucoid flocculi. Colic usually absent. Then vomiting of rice-water material ; agonizing cramps in legs and abdomen, contractions of muscles (recti), collapse, dehydration, shrinkage of tissues, with pinched nose, sunken eyes and shrivelled fingers. Cold, livid, sweat-bedewed skin ; suppression of urine ; cold breath ; whispering voice. Pulse rapid, small, thready; blood pressure very low, sometimes unregistrable. Surface temperature : 94° F. (34·4° C.) ; rectal temperature : 101–105° F. Restlessness ; extreme thirst. Mentality clear at first ; lapses into coma. Death, usually in algid state, but also in stage of reaction, in 2–30 hours ; average 10–12.

Varieties.—

RECOVERY REACTION.—Cessation of vomiting and diarrhœa, re-appearance of pulse, rise of blood pressure, warm skin, secretion of urine ; rapid recovery.

FEBRILE REACTION.—" Cholera typhoid," resembling typhoid ; death from pneumonia or uræmia. Diphtheritic-like inflammation of fauces and genitalia recorded.

HYPERPYREXIA.—Temperature 107–109° F. (41·6–42·7° C.) ; usually fatal. Mild cases—ambulatory cholera (cholerine)—usually at end of epidemic. Mild diarrhœa, no reaction.

CHOLERA SICCA.—No diarrhœa or vomiting, but intense toxæmia, rapidly fatal.

Sequelæ.—Anæmia, physical and mental debility, insomnia. Parotitis, pneumonia, ulceration of cornea, lens-cataract, bedsores and gangrene of extremities. Jaundice frequent. Pregnant women abort, fœtus infected with cholera.

Mortality.—Average about 50 per cent. Varies in different epidemics. Prognosis bad in young and aged, especially if complicated by organic disease and in subjects of malnutrition.

DIAGNOSIS

In epidemics easy on clinical grounds. Symptoms resemble cholera in food poisoning (*cholera nostras*), mushroom, or ptomaine poisoning, subtertian malaria, fulminating bacillary dysentery, trichinosis, arsenical poisoning. In none is mortality so high, or vomit and stools typically rice-water.

Bacteriological diagnosis.—Microscopic detection of vibrios in fæces.

(*a*) Inoculate into alkaline peptone water ; incubate for 7 hours.
(*b*) Examine film for vibrios, in stained films or by hanging drop.
(*c*) Plate out on alkaline agar (Dieudonné's medium).
(*d*) Emulsify colonies and agglutinate with specific serum : positive over 1 : 1,000 diagnostic.

Bandi's method.—Inoculating fæces with alkaline peptone water containing specific serum : clumps visible to naked eye form within 3 hours.

Short method.—Film forming in peptone water emulsified and agglutinated with specific serum on microscopic slide by rotating or rocking (*agglutination forcée*).

Isolation at autopsy.—Tie off sections of small intestine, aspirate contents and inoculate into alkaline peptone water.

Serum agglutination.—Not very satisfactory, not present in acute stage, but in convalescence up to 1 : 1,000. "O" agglutinins most important.

Differential diagnosis.—From food poisoning : in latter, vomiting precedes diarrhœa. Vomit consists of food remains; abdominal pain is severe, tenesmus frequent and colic invariable ; fæces are bile-stained and offensive, but never copious, and urine is never suppressed ; continued pyrexia and no algid stage.

TREATMENT

On general lines as for shock. In premonitory diarrhœa : morphia, gr. ¼, with atropine, gr. 1/100.

Kaolin.—7 oz. in 14 oz. water sipped frequently stops vomiting.

Morphia relieves cramps. Hot water bottles ; foot of bed raised ; warmed bed pan. Suprarenal extract, eucortone (I.V.) 2 c.c. in 100 c.c. of 25 per cent. glucose followed by saline transfusion.

Sulphonamides.—Sulphaguanidine in large doses 0·1 gm. per kg. followed by 0·05 gm. every 4 hours. Initial dose therefore 5 gm. + 2·5 gm. at same periods till symptoms subside. Sulphathiazole and sulphadiazine also active. Condensation product of sulphathiazole and formaldehyde (new compound 6257) strongly recommended. Dose 6 gm. followed by 4 gm., by mouth or rectum. Total 28 gm.

Intravenous salines.—Rogers' hypertonic saline based upon blood pressure and specific gravity of blood. Normal figure for Europeans 1,058; natives, 1,056. Sp. G. of 1,063 dangerous, indicates loss of half blood fluid, requiring injection of 3–6 pints ; subsequent fall indicates further injections. (Sp. G. of blood estimated by bottles of aqueous glycerin ; from 1,048–1,070, drops of blood remain stationary in centre of glycerin solution.)

Composition:

Sodi. chlor.	120 gr. (7·6 gm.)
Potass. chlor.	6 gr. (0·38 gm.)
Calc. chlor.	4 gr. (0·25 gm.)
Water	1 pint (591 c.c.)

at 100° F. (38° C.)

3–6 pints injected slowly, 4 oz. per minute. Continuous drip transfusion apparatus preferable. Blood, plasma, and reconstituted plasma now being used. Modern opinion considers hypertonic saline unphysiological. Now largely replaced by normal saline, drip transfusion—three to four pints necessary at one time.

Routine treatment with potassium permanganate neutralizes cholera toxin : pot. permang. pills, 2 gr., coated with salol, every quarter of an hour for 2 hours, subsequently half hourly till stools become green.

Suppression of urine.—Maintain B.P. Pitressin ½–1 c.c. hypodermically twice daily. Caffeine cit. gr. 5 (0·32 gm.). Tinct. strophanthus, min. 5 (0·3 c.c.). Dry cupping. Intravenous hyperalkaline saline : sodi bicarb, 150 gr. (9·72 gm.), normal saline 1 pint (591 c.c.).

Stage of reaction.—Digitalin gr. 1/100 ; adrenaline 4–6 mgm. Bis. salicyl in large doses. *Antibiotics* have proved disappointing.

Cholera typhoid : treatment as for enteric.

Bacteriophage (choleraphage) treatment : much used in India ; results doubtful.

Anticholera serum : of little value.

Prophylaxis.—*British quarantine system :* detention of cholera ships, isolation of contacts, identification of " carriers," destruction of fomites and general sanitary precautions. In India and Far East, wells and water supplies treated with pot. permang., 60 gr. to gallon. Recently in India, addition of choleraphage to well-water. Results said to be favourable.

Prophylactic inoculation.—Haffkine's vaccine, 4,000 million dead *V. choleræ*, ½ c.c. ; 10 days later 8,000 million, 1 c.c. Slight reaction., Immunity 3–6 months.

Immunization per os (Besredka).—Not favoured by British authorities.

Personal prophylaxis.—General health ; avoid fatigue, chill and excesses, unripe or over-ripe fruit, melons and cucumbers. Boil all drinking water (filtration and chlorination insufficient). Treat all cases of diarrhœa seriously.

ENTERIC FEVERS

Group, known as "enterica," includes fevers due to organisms of genus *Salmonella*.

(1) Typhoid.	*S. typhi.*
(2) Paratyphoid A.	*S. paratyphi A.* (Brion and Kayser).
(3) Paratyphoid B.	*S. paratyphi B.* (Schottmüller).
(4) Paratyphoid C.	*S. paratyphi C.* (Hirschfeld).

GEOGRAPHICAL DISTRIBUTION AND EPIDEMIOLOGY

Typhoid in tropics usually more prevalent in Europeans than in natives; not nearly so common as formerly, probably due to T.A.B. inoculation. Formerly, chief disease of war. Natural immunity of some races, notably Chinese, marked; possibly due to previous infection in childhood. Mortality rate among Europeans in tropics twice that in temperate countries.

Typhoid world-wide ; formerly common in soldiers in India, now rare ; especially met in W. and Central Africa, also paratyphoid. Epidemics in S. Africa and in N. Rhodesia. Prevalent still in Central and S. America, and in the Pacific Isles.

Para A commonest in Asia and Far East (notably India). Para B : Europe, N. Africa (especially in war of 1914–1918). Para C : widespread in B. Guiana and S. America, and in India. Rare elsewhere.

Carriers frequent in urine and fæces. Three types :—

(1) Acute, after attack of enterica.
(2) Chronic, permanently infected. Gall-bladder reservoir. Women 75 per cent. more frequently than men. May also cause cholelithiasis.
(3) Passive carrier, *i.e.*, bacilli in fæces without previous attack of enteric. Especially children.

Transmission.

(1) From infected persons and from carriers, by fingers, food and flies. Food, especially cheese, is common source of Para B.
(2) By contamination of water supply. Under efficient water-carriage system of sewage-disposal risk eliminated ; still exists in more primitive areas.

ÆTIOLOGY

Morphologically similar : Gram-negative bacilli, 2–4 μ by 0·5 μ, actively motile with peritrichous flagella. *S. typhi* grows on ordinary media ; forms acid without gas in glucose, maltose and mannite, slight acidity in milk—non-lactose fermenter ; no indol ; agglutinated by specific serum. A, B and C differ in biochemical and immunity reactions ; form acid and gas in glucose, mannite, maltose and dulcite ; no indol. Para A weaker in fermentative power than B ; permanent acidity in litmus milk. Immunity reactions specific. C shows distinct immunity reactions; some consider it allied to *S. ærtrycke:* others a serological race of B.

Like typhoid, paratyphoid bacilli enter lymphoid Peyer's patches in small and solitary follicles in large intestine, causing necrosis, sloughing, ulceration, then bacillæmia, persisting longer in typhoid than in paratyphoid.

PATHOLOGY

Features common to the group: ulceration of intestine, of Peyer's patches and solitary follicles ; hyperplasia and congestion of abdominal lymphatics and glands ; enlargement and congestion of spleen.

Paratyphoid : sometimes no changes or acutely inflamed ; *large* intestine more frequently ulcerated.

Para C in many instances causes septicæmia with deep metastatic abscesses ; in others it resembles other paratyphoids.

CLINICAL FEATURES

Incubation period : averages 14 days ; may be 7–21. Wide range of severity ; on the whole paratyphoids milder than typhoid. Onset : in paratyphoid often sudden with rigor, headache, anorexia, bone-joint pains and insomnia. Coated tongue ; dry mouth ; moist facies ; general apathy. Epistaxis more common in typhoid than in para. Diarrhœa from commencement, or alternating with constipation. Pulse: dicrotic and relatively slow. Meteorism, + in typhoid; less in para. Enlarged soft spleen on second or third day ; absent in many paras, sometimes in para A. spleen is palpable during convalescence. " Rose spots " on tenth day between costal margin and umbilicus : pale-rose colour, round or lenticular. More profuse in para, especially para A. ; sometimes petechial and resemble typhus. Usually cough and bronchitis. Low muttering delirium and *coma vigil*; not seen in paras. Intestinal hæmorrhage and perforation rare in para.

Typhoid-paratyphoid group characterized by pyrexia of remittent type ending by lysis, low pulse-temperature ratio, toxæmia, splenomegaly and rose-spots (sometimes absent). Pulse rate is 20–40 beats per minute slower than normal pulse-temperature ratio.

Para C., common in S. America, may resemble enteric or be a septicæmia complicated by arthritis, abscesses, cholecystitis and fixation abscesses. Culture of para C. often in abscesses following quinine injections. Mild cases common.

Relapses.—Frequent in para A. ; less common in typhoid and para B.

DIAGNOSIS

Hæmoculture in earlier stages by selective media (tetrathionate broth, Wilson and Blair's medium) ; now possible to obtain positive results throughout whole course of fever. Cultures from blood clot more successful in streptokinase bile broth.

Urine culture.—Bacilluria after 14th day in 15–20 per cent. Catheter or midstream specimen. Selective media : brilliant green, Endo's medium, tetrathionate broth.

Fæces.—With improved methods now much more reliable. Diagnosis most usually successful during first 2 weeks, especially in paras. Concentration medium : tetrathionate broth. Probably superior to Widal test.

Serological diagnosis.—May be complicated in patients previously inoculated with T.A.B. Repeated tests necessary at weekly intervals. Agglutinin fluctuates with clinical data; progressive rise of titre more important than the absolute. Maximum agglutinins between 16 and 24 days. Each infection produces specific agglutinin. In para A. reaction may become positive during convalescence. "H" agglutinin heat-labile; "O" heat stable. Vi (virulence) antigen and antibody now recognized. H agglutinins mostly produced by passive inoculation: O agglutinins (somatic) probably result of active infection with living organisms. All Widal tests must now be made with these different emulsions.

Auxiliary methods.—+ diazo reaction in urine suggestive, also Russo's methylene-blue test.

Differential diagnosis.—From intra-abdominal conditions—diverticulitis, appendicitis—associated with polymorphonuclear leucocytosis (enteric group usually shows leucopenia). From *Bact. coli* septicæmia (often difficult). Typhus difficult to differentiate in early stages, but Weil-Felix reaction conclusive. Enteric fevers often complicated by malaria, bacillary dysentery, etc.

Typhoid from paratyphoid.—No reliable clinical data. In typhoid, mortality 15 per cent. ; in paratyphoid, 2 per cent. ; typhoid more severe and toxic. Relapses in para A. more frequent, longer febrile period than in para B. ; latter often followed by jaundice, thrombosis and suppuration. Para C. diagnosed solely by isolation of organism.

Bacteriophage Method of typing.—Members of the Salmonella group are susceptible to the action of bacteriophages and they are closely related to the type of O antigen present. The Vi antigen of *S. typhi* has a special bacteriophage which attacks it so that anti-Vi-phage grown on typhoid strains of different origin develops a high degree of specificity for this particular strain so that it is possible to obtain a high degree of correlation between the bacteriophage type and the source of the epidemic. Vi antigen present in *S. typhi* and *S. paratyphi* C. and it is probable that *S. paratyphi* A. and B. and *S. typhi-murium* contain Vi antigen specifically susceptible to bacteriophage.

TREATMENT

On general lines. Milk diet during febrile period. Tepid sponging

Chloromycetin (chloramphenicol) in doses of 1·5 gm. daily for 4–5 days apparently cures a large percentage of cases. The temperature defervesces in 4 days, but there is no evidence that it destroys the causative bacilli (*Salmonella*). Recently combination with cortisone advocated—10·7 mg. per kg. for one day. Also combination with minimal doses of aureomycin. Ineffective in carrier state.

Penicillin, in massive doses, combined with maximum amount of sulphathiazole given early in the course of the illness and continued throughout, has also been advocated.

Prophylaxis.—Success of anti-enteric inoculation generally acknowledged. Typhoid now superseded by triple vaccine, T.A.B.: 1,000 million typhoid, 750 million para A, and equal number para B. Two doses of 0·5 c.c. and 1 c.c. injected subcutaneously at interval of 10 days. Reaction slight. Recently 3 injections given at weekly intervals. Para C. also added if necessary. T.A.B.C. vaccine of Vi strains (Felix) now under trial :—

1,000 million .. .. B. typhosus
500 „ .. .. A.B.C. per c.cm.

	1st dose	2nd dose
Adult males	0·25	0·5 c.c.
„ females	0·2	0·4 c.c.
Children		
16–18	0·2	0·4 c.c.
13–15	0·1	0·2 c.c.
9–12	0·05	0·1 c.c.
under 8	0·05	0·05 c.c.

Three weeks' interval between injections. Re-inoculation ("booster," 1 c.c.) advisable one year after primary immunization. Generally considered that protection lasts 3 years.

Hygienic Measures :

(1) Detection of carriers and control.
(2) Protection of water supplies.
(3) Extermination of flies with DDT.

ENTERIC-LIKE FEVERS

Short paratyphoid-like fevers produced by *B. alkaligenes fæcalis*, *B. ærtrycke* and *B. suipestifer; Bacterium coli* infections of urinary tract, especially common in women in tropics. May occasionally assume septicæmic form and organism can be isolated from blood. Rigors closely resemble those of malaria.

Treatment.—Streptomycin probably most effective antibiotic, also chloramphenicol in combination with sulphonamides such as sulphadiazine. Dosages: streptomycin oral, in cachets, 4 gm. daily for 7 days. Sulphadiazine—tablets 0·5 gm. oral. Initial dose 4 gm. followed by 1 gm. every four hours for the same period.

LEPROSY (HANSEN'S DISEASE)

Chronic infective granuloma produced by *Bacillus lepræ*.

GEOGRAPHICAL DISTRIBUTION AND EPIDEMIOLOGY

Formerly world-wide ; now mostly in tropics and subtropics. Lingers in Iceland, Norway, E. Germany, Russia, S. Italy and Greece; very prevalent in India and China (0·5–1 per cent.), Nigeria, Belgian Congo, French Guinea (10 per cent.). More virulent when more recently introduced to Sandwich and Pacific Islands. Rare in children under 2; 44 per cent. of older children living with leper parents develop it in their 10–30th year; rarely after 40. Primitive natives rarely contract it.

Climate : little bearing ; high relative humidity and close contact predispose ; nodular disease more infective.

ÆTIOLOGY

B. lepræ=*Mycobacterium lepræ:* gelatinous capsule ; in shape and size resembles T.B. ; acid-fast, decolourizing more rapidly by alcohol. Occurs in clusters or zoöglœa masses in lymphatic space, arranged like Chinese figures. On whole more squat than T.B.

Demonstrated by biopsy, and in smear preparation from exudate, in all primary deposits in skin in enormous numbers ; in skin macules, in liver, spleen, lymphatics, lungs, endothelium of blood vessels, free in blood, or enclosed in leucocytes. Also commonly in nasal mucus and in nodular leprosy in *apparently normal skin.*

Cultivation.—Has never been proved. Animal inoculation inconclusive. Recent work on hamsters: slow multiplication in tissues after splenectomy.

Differentiation from T.B.—*B. lepræ* group in packets like cigars ; more solid ; rarely show coarse granules ; decolourized by alcohol (with 3 per cent. HCl) in 2 hours ; Gram-positive.

RAT-LEPROSY.—Rats subject to disease by acid-fast bacillus resembling leprosy, in Europe and in tropics. House rats affected : *R. rattus concolor* and *R. decumanus*. Bacillus cultivated in tissue-culture. Subinoculation into hamsters. Distinct from *B. lepræ.*

PATHOLOGY

Specific lesion of leprosy differs from T.B. in blood supply, absence of giant cells and of caseation. In section, leproma shows round cells, with epithelioid and fusiform cells in vicinity of blood vessels ; majority of latter contain leprosy bacilli. Large swollen cells—*globi*—in which *B. lepræ* have died. In maculæ and old lepromata bacilli are scanty and the microscopic picture is that of chronic inflammatory changes in skin papillæ with characteristic foamy degeneration (foam cells of Virchow). In the neural type, fusiform thickening of nerve-trunks ; bacilli in cells, and free between axis cylinders ; eventually nerves become fibrous cords. Tuberculoid lesions contain epithelioid and giant cells.

In nodular leprosy deposits are found in liver, spleen and sometimes lungs, but lepers are often secondarily infected with T.B. Testes atrophy. *B. lepræ* in enlarged hyperplasic lymphatic glands. Lardaceous disease of liver, spleen, kidneys in large proportion of cases of nodular leprosy.

CLINICAL FEATURES

Great variety. Incubation period : difficult to establish ; shortest probably 3 months ; usually 2–10 years ; exceptionally 40.

Primary infection and transmission.—No visible local lesion, but bacillus must enter through breach of surface of skin. Possibly nose forms channel of entrance. Ulceration of septum and epistaxis frequent.

Not hereditary ; children of leprotic parents healthy, if removed early from contact. Leprosy conveyed by actual contact ; most Europeans contract disease by sexual relations with native women.

Prodromata.—Febrile attacks, dowsiness, dyspepsia, diarrhœa or constipation, epistaxis, nasal discharge, pruritus, hyperæsthesia, pins and needles. Areas of sweat-suppression (anidrosis), also excessive sweating coming on with slight provocation.

Primary exanthem.—Evanescent fever and skin eruptions, erythematous patches, later pigmented, may be vitiliginous or bullæ with paræsthesia. Loss of hair (depilation) ; scalp rarely, if ever, affected. Eyebrows and eyelashes often tend to be patchy. Primary lesions on face, forehead, nose, cheeks, ears, extensor surface of limbs. Palms and soles seldom attacked. Mucous membrance not affected. Stage of deposit in skin=nodular ; in nerve-trunk=nerve or anæsthetic leprosy. Mixed forms also.

Classification now founded on resistance of tissues to leprosy bacillus. Low resistance produces definite histological picture of leproma. High resistance produces *tuberculoid*. Prelepromatous and pretuberculoid period, in which reaction to bacilli is slight, known as *indeterminate*. Subclassification accordinly of *lepromatous* which is macular, infiltrated, nodular, neural and generalized, of *indeterminate* which is macular, neural, and neuro-muscular: of *tuberculoid* macular, papular and neural.

Lepromatous or Nodular form.—This is the severe type.

Well-marked macular stage. " Leproma " formed in infiltration with round cells, in size from pea to plaque many inches in diameter ; red, brown or yellow—usually ham-coloured in white people. Centre is anæsthetic to pain and heat, devoid of hair, greasy-looking, due to blockage of sebaceous follicles ; round or oval, but many coalesce, forming irregular patches ; obliterate natural folds of skin on face causing repulsive leonine appearance. Nodules on back of hands and extensor surface of arms. New crops appear and finally soften in centre which is absorbed, leaving smooth, circular scar tissue ; or may ulcerate and discharge yellow pus. Septum of nose often destroyed. Lepromata on conjunctiva spread to cornea and anterior chamber, with destruction of iris and ciliary body. Termination: usually secondary infection (T.B., pneumonia, bacillary dysentery). Bacillæmia common in advanced cases. Hæmagglutination and hæmolytic titres are highest in this type.

Tuberculoid type is really the mild type. The term tuberculoid is used on account of resemblance to tuberculosis. Clinical course depends upon resistance. Characteristic clinical feature is " tubercle " raised above skin surface and dark in colour. Tuberculoid skin lesions have sensory changes in tactile pain and heat sensation with suppression of sweat.

Nerve leprosy.—Prodromal macular stage usually slight or absent. When severe : annular, macular somewhat raised lesions, resembling ringworm. Bullæ (*pemphigus leprosus*) on hands, feet, knees, etc., burst and are converted into anæsthetic patches. Implication of nerves : neuralgic pains, formication, hyperæsthesia, anæsthesia, lymphadenitis. Leprotic fever ; then trophic changes in skin, muscle, bone. Fusiform swelling as thick as little finger on ulnar or other nerves ; anterior tibial, peroneal, median, radial, brachial and, commonly, great auricular and cervical nerves can be felt and seen lying close under skin ; at first tender on pressure, become entirely anæsthetic. Symmetry of anæsthetic areas. Temperature of digits affected : 2–3° F. lower than normal. Atrophy of subjacent muscles supplied by thickened nerves, with corresponding distortion and loss of power. Gradual contraction of fingers causes *main-en-griffe*. Eyelids droop, lower everts ; lachrymation ; then destruction of lachrymal gland. Ulceration and leucoma of cornea ; blindness. Paralysis of lips causing salivation. Anæsthetic patches on limbs crack and ulcerate. Deformity of nails, which become like talons. Ulceration of exposed parts ; rarefying osteitis ; destruction of toes and fingers ; absorption of phalanges ; perforating ulcer of soles of feet. Progress very slow. Stenosis of larynx produces leper cough and voice.

Lepride.—Diffuse cutaneous rashes resembling tuberculides, probably allergic.

Lepra reaction (*Erythema nodosum*) acute with fever in which all lesions become swollen and inflamed, usually when infection has become generalized and advanced. At same time fresh nodules or macules appear, cutaneous and subcutaneous nodules become pustular and discharge pus containing *B. lepræ*. Reaction may last few days or may be prolonged for weeks. Concurrent disease may light up lepra reaction. Process may spread to nerve-trunks and ramifications. Nerves become congested and tender.

DIAGNOSIS

Anæsthetic patches, especially in centre of macula. *Early deposits on forehead;* thickening of nasolabial fold. Hypertrophy of nipple in men. Demonstration of *B. lepræ* (acid-fast bacilli) in nasal mucus ; typical morphology and disposition. *All acid-fast bacilli in nasal mucus not necessarily B. lepræ.* Biopsy of skin lesions; smear preparations. Blister of skin by carbon-dioxide snow and demonstration of *B. lepræ* in serum; also thick-drop blood preparations dehæmoglobinized, fixed and stained for *B. lepræ.*

Blood sedimentation.—Rate invariably increased ; Westergren's method (citrated blood in Wintrobe's tubes ; at end of hour, measure column of plasma left clear by sinking of r.b.c.).

Rubino's reaction.—Agglutination-sedimentation test with formolized sheep's corpuscles. Rapid agglutination and sedimentation in less than 1 hour characteristic of leprosy.

In absence of syphilis pseudopositive W.R. reactions in 63 per cent. nodular, and 27 per cent. anæsthetic cases; but syphilis may coexist.

Intradermal Mitsuda (lepromin) **reaction** : with extracts of lepromatous material ; histologically resembles Mantoux test in T.B. Material obtained by removing large, soft nodules, boiling in water and divided into small fragments with scissors, dried for few hours and dessicated over pure sulphuric acid. 0·4 gm. of dried powder is ground up with 10 c.c. saline and fluid pipetted off and carbolic acid 0·5 c.c. added. Suspension made up in 1 c.c. ampoules sealed and heated at 120° C. for half an hour. A series of intradermal tests with full strength lepromin are made in dilutions of 1 : 2, 1 : 4 and 1 : 8. The skin on inner aspect of arm is chosen and the dose is 0·2 c.c. intradermally. The lepromin reaction is of use as a means of testing natural resistance to leprous infection, the higher the reading the better the chances of recovery. B.C.G. orally converts lepromin-negative to positive more frequently than tuberculin-negative to positive.

Histamine test.—Production of histamine in tissues by pinching skin with finger nail. Where cutaneous nerves are affected by leprosy the erythematous reaction does not appear in early leprous lesions, but shows up as white patches on an erythematous skin.

Differential diagnosis.—From leucoderma, or vitiligo ; mistake often made ; no anæsthesia in leucoderma. From sensory trophic lesions of syringomyelia, spina bifida or hypertrophic polyneuritis with flaccid paralysis of hands and thickened nerve trunks. From progressive muscular atrophy, lupus, tuberculides (inoculation of guinea-pig). From other skin diseases : acrodynia, syphilis, erythema nodosum and multiforme, ringworms, pellagra, filarial elephantiasis (*N.B.*, elephantoid condition may complicate leprosy), mycosis fungoides. In. S. America from Espundia (nasopharyngeal leishmaniasis).

Prognosis.—Complete recovery exceptional. Depends to some extent on nutrition and climate (worse in very cold or hot countries). In nerve leprosy, bacilli may die out. Disease, as in T.B., burns itself out ; therefore disease may be arrested. Lepers may live 30–40 years. Nodular form runs a more acute course. Lepers die from nephritis or lardaceous disease, stenosis of larynx, pneumonia. Galloping leprosy : death within one year.

TREATMENT

Depends upon physical condition, nutrition and hygienic surroundings.

Sulphones cause striking improvement especially in early tuberculoid cases, and even in chronic nodular leprosy, as well as in ocular leprosy:—D.D.S. or dapsone (diamidodiphenyl sulphone), promin, promizole and diasone. Careful supervision necessary on account of iron-deficient anæmia. Commence with small doses (5 gr.) (0·32 gm.) in capsules or tablets. With hæmoglobin 70 per cent. commence with 1, 2, 3 tablets according to the general condition of patient (tablets = 100 mg.). Initial dose repeated every second day for first week till patient is taking 3 tablets daily for six days a week. Iron and liver treatment whenever necessary. Maximum average dose is 6 tablets daily for 6 days a week for 3 weeks in every month. Prominent nodules and other skin lesions gradually absorbed with gradual diminution in number of bacilli. Most striking improvement in eyes, especially cornea. Cases with negative "lepromin reaction" become positive.

Treatment continued till bacteriological examination negative over period 6 months to 2 years. Total length may be 4–5 years. Promizole less toxic and quicker in action than promin.

Standard induction of treatment is as follows:—

100 mg. Dapsone twice weekly for 3 weeks.
200 mg. „ „ „ „ 3 „
300 mg. „ „ „ „ 3 „
400 mg. maximum.

For those with reactions a maximum of 200 mg. for at least three months is advised.

Isoniazid (isonicotinic acid hydrazide—INH), 6–8 mg. per kg., given in combination with dapsone, is considered beneficial over a period of 2–3 months.

Thiacetazone (thiosemicarbazone—TB); no relationship to sulphones. Advocated to those intolerant of sulphones. Dose 25 mg. daily, increasing each week by 25 mg. till 150 mg. Children under 12 half-dose. Effective also in tuberculosis.

Reactions.—Lepra reaction occurs mainly in severe lepromatous patients. Treatment is by stibophen injections and reduction of dapsone. Lepromatous nerve reactions occur mostly when bacteriological smears become negative and give rise to thickened nerves and intractable pain. Injections of procaine give relief. Tuberculoid nerve reactions are infrequent and are due to caseation. Residual hypopigmentation may be mistaken for active leprosy. Dermatitis is associated with hepatitis and may lead to cirrhosis. Anæmia may occur and is counteracted by ferrous sulphate.

Ephedrine.—2 gr. in gelatine capsules by mouth relieves nerve pains.

Carbon dioxide snow.—Local application sometimes beneficial.

Intranasal therapy.—For nasal ulceration: ionization of infected mucosa.

Co-existing syphilis important.—Treat with salvarsan, pot. iod. and penicillin.

Surgical measures.—

Eyes. Division of cornea on pupillary side of lesion prevents extension. Tarsorrhaphy for eversion of lids. Iridectomy for iritis.

Tracheotomy for laryngeal stenosis.

Sequestrotomy for necrosis of bone.

Amputation for septic ulceration of leg and perforating ulcer.

Prophylaxis.—Segregation and isolation of lepers, especially in infective state. Organisation of leprosaria. *Model:* Culion Island Leper Colony in Philippines ; complete with laundry, church, school, etc. Much depends on social surroundings. Segregation of children of leprous parents. Lepers prohibited from selling or handling food, laundry work, peddling or prostitution. Prophylactic inoculation with B.C.G. being tried out.

ULCERATING GRANULOMA OF PUDENDA

GRANULOMA VENEREUM (DONOVANOSIS)

Infectious disease transmitted by sexual contact and auto-inoculation.

Geographical distribution and epidemiology.—Widespread in tropics, India, Guiana, Brazil, S. America, South U.S.A., West Indies, New Guinea, Pacific Islands, N. Australia, W. Coast of Africa, S. China.

Never seen before puberty ; 14–50 ; in both sexes, especially in women when polyandry is practised.

Ætiology.—Venereal infection with intracellular organism, *Calymmatobacterium granulomatis* (Donovan) (according to modern terminology—*Klebsiella inguinale*) and, possibly, an intracellular diplococcus (*B. mucosus capsulatus*). Non-hæmolytic streptococcus frequent secondary invader (Meleney).

Pathology.—Histologically allied to rhinoscleroma. Nodules at margins of sores ; masses of inflated round, mononuclear cells in Malpighian layer. Probably derived from plasma cell containing the organisms, demonstrated by Dieterle silver impregnation. Vascular growths without hæmorrhages, round sebaceous follicles, blood vessels, lymphatics and sweat glands, especially hair follicles.

Clinical features.—Incubation period short : 2–8 days after sexual contact may be prolonged to 12 weeks. Primary lesion in genitalia, penis, labia majora, pubes or groin. Nodular thickening of skin. May occur on face, hands or abdomen. Excoriates easily, exposing granular bleeding surface. Extends by peripheral spread and by auto-infection of opposing surfaces. Predilection for warm, moist, surfaces such as scrotum, labia, flexures of thighs. Very slow ; several years to affect large areas. Healing by depigmented, atrophic scar.

In female : clitoris, vagina, labia ; sterility produced. Extends to perineum and rectum : profuse acrid-smelling discharge. No involvement of lymphatic glands. Blockage of lymph channels produces elephantiasis of genitalia, stricture of urethra and recto-vaginal fistulæ. May ulcerate through abdominal wall and invade bladder.

Metastatic lesions have been described in Madras in the liver (Rajam) and the organisms have been recovered from this organ. Thierfelder has found them in nose, ear, forehead and mandible. Localized deposits have occurred in the middle ear and mastoid process.

Diagnosis.—By clinical appearance and demonstration of histological picture. Often mistaken for syphilis, but does not react to antisyphilitic treatment. W.R. negative.

Differential diagnosis : from lupus vulgaris, syphilis ; fungating form in negroes resembles carcinoma or epithelioma, gonorrhœal endocervicitis or erosion of cervix.

Treatment.—Scraping and cautery in early stage. Excision of primary lesion. Subsequent X-ray treatment. Antibiotics have now replaced older treatments with antimony preparations and sulphonamides.

Streptomycin by injection probably most effective, given intramuscularly, in divided doses four-hourly up to 4 gm. daily for five days. Side-effects such as cylinduria and vestibar dysfunction have been recorded. Dihydro-streptomycin probably better. Aureomycin and chloramphenicol also useful. Former in total dosage of 20 gm. in 10 days.

Infection with non-hæmolytic, anaërobic streptococcus (Meleney); standardized preparation of zinc peroxide rubbed daily into fistulæ and ulcerations, introduced by fine catheter.

Prophylaxis.—Spread by sexual contact. Prohibit intercourse with native women.

TROPICAL PYOMYOSITIS

Pyæmia associated with deep-seated intramuscular abscesses common in tropical residents.

Geographical distribution.—In almost every tropical country, especially in Pacific Islands, West Indies, W. Africa, Brazil, Dutch East Indies. Has occurred as epidemic in W. Indies.

Ætiology.—Somewhat similar abscesses with *Wuchereria bancrofti* infections, but occur also in countries from which this parasite is absent. Probably hæmolytic form of *Staphylococcus pyogenes aureus* ; occasionally *Streptococcus pyogenes*. Other associated diseases : ancylostomiasis, syphilis, malaria.

Clinical features.—Types : acute non-suppurative ; acute suppurative with relapses; acute suppurative with pyæmia. Indurated, painful, inflammatory swellings filled with serous fluid, or extensive deep suppuration, in gastrocnemius, popliteal space, thigh muscles, serratus magnus, latissimus dorsi ; often associated with synovitis of knee joints.

Diagnosis.—By aspiration of pus and isolation of staphylococcus. Differentiation from gumma, filarial abscess, glanders, melioidosis, possibly plague and trichinosis. Polymorphonuclear leucocytosis 15–20,000.

Treatment.—Incision and drainage. Penicillin injections in large doses. *Sulphonamides*. Sulphadiazine 1·5–3 gm. (23–46 gr.) daily for 10 days; also sulphapyridine and sulphathiazole.

RHINOSCLEROMA

Geographical distribution.—World-wide ; commoner in tropics in foci, E. Europe, Turkestan, India, Java, Sumatra, Morocco, Egypt, Cuba, Mexico, S. America.

Ætiology.—*Klebsiell arhinoscleromatis*, related to *Streptococcus pneumoniæ*; Gram-negative, easily cultured; forms know-like growths on gelatin or agar; coagulates milk and forms acid with lactose. In sections, hard, fibrotic swellings of low order of pathogenicity. To be differentiated from other encapsulated pneumococci.

Pathology.—Characterized by peculiar plasma-cell infiltration " foam cells " (Mikulicz cells) and Gram-positive hyaline droplets (Russell's bodies). Nodules never break down, but become sclerosed.

Clinical features.—Characteristic appearance : spontaneous, painless, chronic inflammation from nostrils to hilum of lung. Gross deformity of nose (Hebra nose) narrowing of nasal passages, perforation of nasal septum, destruction of uvula. Metastases in lymphatic glands. General health good.

Treatment.—Mainly surgical. X-ray therapy. Inoculated malaria and protein-shock therapy. Associated febrile disease curative : erysipelas, typhoid or typhus.

VELD SORE

Septic or desert sore (cutaneous diphtheria). Ulceration of exposed parts in desert areas. Queensland, N. Australia, S. Africa, Egypt, Palestine, Syria, Libya, E. Africa, Iraq.

Ætiology.—Most cases primarily caused by diphtheria bacillus. Discovered in 1901 (H. Scott), confirmed in both world wars. In initial bullous stage Klebs-Löffler bacilli demonstrable in fluid. Pathogenic for guinea-pigs, neutralized by anti-diphtheritic serum. Similar infected sores found on horses and camels.

Clinical features.—Amongst British troops in first world war, most frequently in cavalry and camel corps; coincided with widespread faucial diphtheria. Sores on parts exposed to injury: arm, elbow, knee, face, eyebrow, cheeks, often at site of abrasions.

Vesicle painful, straw-coloured fluid round hair follicle. Bursting leaves shallow ulcer and raw, tender surface. Then chronic stage : punched-out circular ulcers with undermined edges, thickened margins and cyanotic appearance. Associated with paralyses—especially accommodation palsy during second week—and polyneuritis (with loss of deep reflexes in 3 weeks). Initial local palsy determined by site of local lesion ; in Palestine anatomical relationship between diphtheritic lesion and palsy became clear. Direct passage of toxins from lesions along neural channels to C.N.S.

Diagnosis.—By appearance of sore and isolation of Klebs-Löffler bacillus. Polyneuritis to be distinguished from other forms of neuritis, tabes, and beriberi.

Treatment.—Clean up sore with eusol dressings ; elastoplast strip. Anti-diphtheritic serum, 4,000 units, injected in vicinity of sores. In chronic stage : sulphonamide paste. Acriflavine ointment, 0·1 per cent. in *adeps lanæ* ; to this may be added 10 per cent. sodi. sulph. for osmotic effect; penicillin.

Prophylaxis.—Protection of skin against abrasion. In mechanized units grease on skin protects against these sores.

CHAPTER V

VIRUS DISEASES

Preliminary.—Filterable ultramicroscopic particles, can be photographed by ultraviolet light and special optical apparatus. Larger particles (psittacosis, vaccinia) can be stained and measured. Many virus diseases of plants, birds and animals. All viruses associated with living cells and *in vitro* require them for multiplication ; stimulation of physiology results in active multiplication of cells, followed by depression, as in cell necrosis of liver in yellow fever. Resistance of body to bacterial invasion consequently reduced. Specific action may be restricted to cells of one particular organ, *e.g.*, rabies for cells of C.N.S. Inclusion bodies in infected cells intracytoplasmic or intranuclear ; stain intensely with acid dyes (eosin). Cultivation (not possible in absence of living cells) on minced chicken embryo in Tyrode's medium, or inoculation of virus on chorio-allantoic membrane of chick embryo.

Approximate size of virus particles obtained by filtration through gradocol membrane :—

Yellow fever	18 mμ– 27 mμ
Rift Valley fever	23 mμ– 35 mμ
Psittacosis	220 mμ–330 mμ
Rabies	100 mμ–150 mμ
Vaccinia	125 mμ–150 mμ

mμ = 0·001 μ

Resistance: to heat varies ; extremely resistant to cold ; survives for months dried. Rabies virus resistant to glycerin. Inactivated by action of dyes, methylene blue. Recovery from virus infection associated with long immunity.

YELLOW FEVER: " AMARYL " (International Nomenclature)

Acute febrile disease, endemic or epidemic, due to filterable virus, with peculiar limited distribution. For the most part conveyed by domestic mosquito, *Aëdes ægypti*.

GEOGRAPHICAL DISTRIBUTION AND EPIDEMIOLOGY

More extensive than formerly supposed. Exact range determined by *mouse-protection* test. Formerly extensive, virulent epidemics throughout W. Coast Africa, Mexico, S. America, West Indies. Formerly introduced into Europe. Special primitive form—jungle yellow fever—recognized since 1930. Considered in 1925 to have disappeared from S. America—not correct. Virus exists still in large areas of Brazil, Colombia, Peru and Central America. Recent epidemic in Trinidad accompanied by death of numbers of red howler monkeys (1954). Since 1948 smouldering epidemic of "jungle" yellow fever has been spreading through Central America. Commencing in E. Panama it has spread at the rate of 13 miles per month to Nicaragua and Costa Rica to Mexico. During the last two years it appears to have fizzled out, but in 1956 there has been a recrudescence. In Africa the limit extends from W. Coast, latitude 15° N., along S. border of Sahara to Blue Nile to Eritræa-Massawa and the Red Sea coast, thence southward including Somaliland, Ethiopia and Kenya Colony to the N. shores of L. Victoria. Thence skirting the E. borders of Belgian Congo, to a line running through N. Rhodesia to Angola. Area extends over 4 million sq. miles. Islands in Gulf of Guinea included. Extensive epidemic in Nuba Mts., S. Sudan (1940): 17,000 cases, many deaths; in area where not previously noted. Danger of transportation in epidemic form by airplane to India or China, where disease is unknown.

Three epidemiological types :—

(1) Urban, epidemic, transmitted by *Aëdes ægypti*.
(2) Rural, epidemic, transmitted by *A. ægypti*.
(3) Rural, endemic (jungle yellow fever), transmitted by jungle mosquitoes (S. America and now W. and C. Africa).

In (1) and (2) epidemic continues till either all infected mosquitoes are destroyed, or high percentage of *susceptible* population become immunized to the virus. It therefore follows that the area with a population immune to yellow fever is vastly greater and overlaps the area in which the actual disease "yellow fever" can be said to exist. Hence sudden outbreaks which occur from time to time in W. Africa. In endemic area disease is present in slight, unrecognizable form.

Virus of yellow fever readily transmitted, but for development in epidemic form requires mean temperature of over 75° F. (24° C.). Never extends beyond lat. 40° N. and 35° S. Dampness favours spread, especially rainy season ; occasionally occurs in arid areas and up to 4,000 ft.

Jungle yellow fever in S. America, Bolivia, Colombia, Brazil, now W. Africa, Ugânda, N. Kenya and Congo, conveyed by bites of jungle mosquitoes.

Reservoir hosts.—Recent evidence points to possibility, especially in S. America, that red howler monkeys (*Aloutta seniculus* or *A. stentor*) are reservoir; outbreaks associated with great mortality in them. Virus also found in blood of wild animals in S. America, opossums, edentates some rodents. In C. and S. America monkeys of genus Cebus and Ateles (spider monkey), the squirrel monkey—(*Saimiri*) and in Colombia the Douroucouli (*Aotus*). In Central Africa Waldron's Colobus and the " Bush Baby " (*Galago crassicaudatus*). African relatively immune, but Indian monkeys (*Macaca*) very susceptible—useful laboratory animal. Hedgehogs, especially Pruner's hedgehog in Sudan, very susceptible.

ÆTIOLOGY

Virulent virus isolated and now maintained in laboratory. From blood and liver of infected monkeys (*Macaca*) ; maintains virulence when frozen or dried. Present in blood of yellow fever cases for first 5 days. Infection can be acquired from blood of patients (as in act of blood examination) ; doctors have died from making autopsy on case. *Macaca rhesus*, artificially infected with active virus, dies in 4–7 days. Tissues infective, and yellow fever has been contracted by laboratory workers engaged in dissecting them. Virus can pass through unbroken skin, conjunctiva and nasal mucosa, and in monkeys through intestinal mucosa. Virus divisible into (*a*) neurotropic, (*b*) viscerotropic forms.

Neurotropic.—White mice injected by intracerebral inoculation develop meningo-encephalitis; when passed in this form to other mice becomes stabilized. Does not produce general picture of yellow fever, but occasionally may revert to viscerotropic form.

Viscerotropic.—From monkey to monkey, reproduces clinical picture of yellow fever.

Immunity.—Immune bodies produced in serum of recovered patients protect for life. Such serum neutralizes definite amount of virus ; when injected into susceptible animal infection does not occur. " Protection tests " based on this.

Monkey protection test.—Serum and virus injected into rhesus monkey ; if serum contains sufficient immune body, death does not result.

Mouse protection test.—When neurotropic virus used, mixture of serum and infected mouse brain injected intraperitoneally into mice (inoculated intracerebrally with starch) ; if serum fails to protect, animal develops encephalitis. This method widely employed in yellow fever surveys.

Cultivation.—Neurotropic form cultivated in minced chick-embryo and on chorio-allantoic membrane of chick.

Natural transmission.—Optimum temperature for development of virus in *Aëdes ægypti* is 26° C. (78·8° F.) (extremes 18–37° C.). Percentage of mosquitoes becoming infected very small. 0·01 c.c. of blood imbibed. Inoculation period, before mosquito is infective, at 37° C. (98·6° F.), 4 days ; at 21° C. (69·8° F.), 18 days. At 10–15° C. (50–59° F.) virus persists, but bites are not infective. Exact course of development in mosquito uncertain ; present in alimentary canal for 10 days ; undergoes multiplication ; salivary glands infected.

Female *A. ægypti* alone conveys yellow fever ; strictly nocturnal in habit. Eggs deposited 3 days after feeding. Virus not hereditarily conveyed through mosquito to eggs. Experimental transmission to man by mosquito effected.

Mosquito.—*Aëdes ægypti*, "Tiger mosquito," black and white, striped appearance, lyre-shaped device on thorax, short palpi, head covered with broad, flat scales, large, retractile 8th abdominal segment. Eggs laid separately, each surrounded by small air-chamber. Can withstand desiccation ; larvæ vertical in water ; short respiratory siphon, twice as long as broad ; hair tuft in centre of siphon comb. Occurs all over tropics, 48° N. and S. of equator. Domestic ; never breeds more than 100 yards from houses ; eggs deposited in small, dark receptacles, in tree holes, tins, coconut shells, sagging eaves, tops of pineapples, sisal leaves, cemeteries, ships' bilges, beer bottles, old car tyres. Eggs white at first, become black ; larvæ hatch in 12 hours, eggs resist drying for 6 months.

Other mosquitoes.—Other species of *Aedes* can transmit yellow fever under laboratory conditions. *Tæniorhynchus africanus* possibly a vector in S. Sudan ; others suspected there. "Jungle yellow fever" transmitted by *A. leucocelænus*, *Hæmagogus capricorni*, *H. spegazzini falco* and (?) *Sabethini* in S. America (Colombia); by *A. simpsoni* in Ituri forest, C. Africa. *Hæmagogus* and *A. simpsoni* are inhabitants of tree tops; absent in catches at ground level. Jungle mosquitoes transmit virus to monkeys, then conveyed from them by *A. ægypti* to man.

Incubation period.—1–6 days in man ; 14 days between first case and outbreak of epidemic = period of development in *Aëdes*.

Facts explain :—

(1) Non-transmission of yellow fever to contacts from patient outside endemic area.
(2) Danger of visiting endemic area when mosquitoes are active.
(3) Incubation period of epidemic.
(4) Clinging of yellow fever infection to ships, buildings, etc.
(5) High atmospheric temperature necessary for epidemic of yellow fever.

PATHOLOGY

Saffron or olive-yellow skin. Rigor mortis marked. Petechiæ on skin and mucosa. Brain and meninges hyperæmic. Cartilages intense yellow. Blood dark, firmly coagulated ; passive hæmorrhages ; stomach contains dark, black blood ; ecchymoses in mucosa. Virus has selective action on liver cells ; liver box-wood colour ; mid-zonal necrosis; hyaline cytoplasmic degeneration. Councilman lesions; nucleoplasm contains acidophilic intranuclear masses (Torres bodies). Coagulative necrosis with marked edge surrounded by narrow clear halo; fatty degeneration of parenchyma cells, giving a salt and pepper appearance in sections stained with hæmatoxylin and eosin. Kidneys : cloudy swelling, tubules filled with casts and desquamated epithelium ; lime casts in convoluted tubules.

CLINICAL FEATURES

Great variety. In immune or partially immune population may be slight, like influenza. Onset: sudden rigor, not usually high pyrexia. Attack: 3 stages: (1) initial fever, (2) period of calm, (3) reaction.

(1) **Initial.**—3–4 days. Maximum temperature 2nd day, 104° F. (40° C.) ; temperature 98–99° F. (37–37·5° C.) on 3rd, 4th and 5th days. Rarely, maximum temperature not reached till 8th day. Supraorbital headache severe ; photophobia. Severe backache (as in smallpox). Bone pains ; epigastric pain. Face flushed, swollen. Eyes injected, " ferrety." Skin dry. Restlessness. Pulse 100–120, bounding. *Faget's sign* : falling pulse-rate with constant T., or constant pulse with rising T. Tongue : white, central coating, sides clear, small, pointed ; palate : congested, swollen ; gums swollen, bleeding. Bowels constipated.

(2) **Calm.**—Congestion of face subsides, eyes sunken, eyelids show ecchymoses. Bradycardia : 30–40. Skin moist, clammy. Hæmolytic icterus, 3rd day ; scleræ and skin golden yellow (" yellow " fever), but not in mild cases, where colour is saffron to mahogany brown ; icterus persists through fever into convalescence. Skin has peculiar odour—" gun washings," " fish market " ; often deep blue spots—subcutaneous effusions—or sometimes erythematous, papular and other eruptions. Erythematous congestion of scrotum and vulva pathognomonic. Diarrhœa ; often melæna. Albumin in urine ; tendency to anuria on 2nd day; in severe cases oliguria, with albumin + (2 gm. per litre). The more pronounced the graver the prognosis. Urine-urea 0·15 gm. per cent. ; blood urea raised ; urine acid ; granular casts. Hæmoglobin (spectroscopic), bile pigments, 5th day. Hæmaturia occasionally. Insomnia invariable ; delirium sometimes ; torpor ; in severe cases, coma, subsultus. Sudden rise of temperature presages death. Frontal tâche cerebrale visible.

Nausea and *vomiting* more frequent than in other fevers : (*a*) bilious, (*b*) hæmorrhagic, " black vomit," coffee-grounds ; projectile, painless. Disintegrated r.b.c. and hæmoglobin in intensely acid yellowish fluid. Transudation of blood through gastric mucosa ; sometimes hæmatemesis. Often hæmorrhages from ears, nose, eyes, mouth, bladder, uterus. " Everything congested at onset, everything bleeds at end." Death usual on 5th–6th day ; seldom before 3rd. Sudden fall of temperature after 11th day is serious. Period of calm may lead to convalescence. Headache, back, and bone pain, photophobia, prostration. Recovery usually rapid.

(3) **Reaction,** in severe cases.—Temperature rises, but not so high as initial fever. Pronounced icterus, black vomit, suppression of urine, stupor, coma, often abscesses, parotitis, or acute hepatitis. Spleen not enlarged. May terminate in crisis. Sweating +. *Relapses* rare—dangerous. No anæmia ; initial leucocytosis, then leucopenia, 5th–6th day. Polymorphs predominate, then mononuclears. Virus in blood for first 108 hours but has been isolated on 12th day of disease; antibody formed in 83 hours. Plasma prothrombin shows definite relationship to the severity of the disease. Average prothrombin percentage is 66·7.

DIAGNOSIS

Easy in epidemic: difficult in isolated cases. Several deaths with black vomit in limited area in quick succession suggestive. Albuminuria important. Modern laboratory methods ; mouse and monkey inoculation positive. Suspected blood keeps infectivity for weeks in ice-chest. In fatal cases liver changes diagnostic. In native races, where autopsies not permitted, *viscerotome* employed (instrument for obtaining specimens of liver from cadavers for microscopic section).

Differential diagnosis.—From subtertian malaria, bilious remittent form. Discovery of parasite, pigmented corpuscles, splenomegaly, *but* in Europeans in W. Africa the two diseases may co-exist. Sometimes to be differentiated from blackwater on account of hæmoglobinuria. From infective jaundice (Weil's disease) : not easy, often confused. From infective hepatitis (no albuminuria). Dengue in early stages closely resembles yellow fever, but not so severe. Other little-known virus diseases in Tunis, Nigeria, French W. Africa, Belgian Congo, Uganda and Colombia, S. America may produce fever and jaundice.

Mortality and prognosis.—Prognosis good, if temperature in initial fever does not exceed 105° F. Better for women and children than for men; for residents than newcomers; worse for alcoholics. No deaths in cases with fever under 103° F. ; no recoveries with temperature over 106° F. (41° C.). In some epidemics, mortality 50 per cent. In natives of endemic zone much less : 7–10 per cent. Ambulatory cases quite common.

TREATMENT

Strict bed. Good nursing. Injection of immune serum of little value (virus in blood neutralized by immune bodies 4th and 5th day). Purgative at onset (ol. ric. or calomel 2 gr.). Hot bed baths and sponging, and mustard plasters to epigastrium relieve vomiting and headache. Cold bath and sponging for hyperpyrexia. Repeated doses of iron perchloride for black vomit. Suggested that vitamin K may be useful. Calcium lactate in large, repeated doses counteracts excess of guanidine in blood. For liver necrosis : glucose D, repeated doses by mouth, or 5 per cent. intravenously with injections of insulin, 5 units. For restlessness : luminal, phenacetin, antipyrine. In period of calm : alcohol, champagne in sips, brandy. Free fluids for oliguria.

Diet.—Liquids only during anorexia ; afterwards albumin water, iced milk or broth. If vomiting persistent, nutrient enemata. Sternberg treatment counteracts hyperacidity, much employed : sodi bicarb. 150 gr. (9·7 gm.), perchloride of mercury ⅓ gr. (21 mgm.), water 2 pints (1,180 c.c.) ; 1½ oz. every hour.

N.B.—Suspected cases of yellow fever in endemic area must be nursed under mosquito net, or in mosquito-proof room.

Prophylaxis.—Destruction of mosquitoes—especially *A. ægypti*—and prevention of breeding by every measure ; Public Health order ; fines for neglect. Introduction of " millions " (*Gambusia*) and goldfish in reservoirs, water butts, etc. Cisterns screened with fine-mesh metallic gauze. All stagnant water abolished ; holes in trees cemented. Empty tins rolled out by steam-roller. "*Flit*" for destruction of adult Aëdes. DDT has been employed with much success especially in form of residual sprays. In most S. American towns *A. ægypti* have been exterminated by these means. Bilge water pumped out of ships ; fumigation ; quarantine in port.

International Aerial Convention for aircraft : crews and passengers free from risk of infection 6 days or have been inoculated or have had disease. "Anti-amaryl" aerodromes specified. Fumigation of aircraft by "Deskito" (pyrethrins in glucose)—non-toxic ; 1 : 30 dilution in water ; 150 c.c. for each 100 cu. feet.

Prophylactic inoculation.—Successful in S. America and W. Africa Virus grown on minced chick embryo with Tyrode solution ; then inoculated into eggs with 8–9 day embryo for 4 days at 37° C. (98·6° F.) ; ground-up vaccine prepared.* Attenuated pantropic virus employed (17.D). Reactions now very slight. Immune bodies in serum 12–14 days, usually 21. Present in some cases for 7 years, sometimes absent in 6 months. Re-inoculation every 5 years advisable. Immunized persons not infective for *Aëdes* mosquitoes. Infants under six months liable to develop meningo-encephalitis, usually transient; also occurs with French Dakar virus inoculated by scarification.

RIFT VALLEY FEVER

Epidemic disease of sheep in Kenya, occasionally transmitted to man.

Geographical distribution and epidemiology.—First described in 1931 during outbreak amongst sheep and lambs at Naivasha, Kenya (5,500–6,000 ft.) with focal necrosis of liver. Europeans in contact developed dengue-like fever.

Ætiology.—Virus from blood, preserved in oxalate-carbol-glycerin, was brought to England where lambs were infected and those in contact also developed fever. Virus particles, 23–35 mμ, found in blood, liver, spleen, but not in urine. Can pass through placenta and infect fœtus. In oxalate-carbol-glycerin at 4° C. retains virulence for 8 months. Can be cultivated like yellow fever on minced chicken embryo and on chorio-allantoic membrane. Neurotropic strain produced by intracerebral inoculation of mice. Pathogenic for monkeys and many rodents ; with mouse-protection test as for yellow fever. Immune bodies present in natives of S. Sudan, N. Uganda and French Equatorial Africa. Virus is present in blood for 6 days, then neutralized by immune bodies in serum, as in yellow fever. Virus pathogenic to small rodents and S. American monkeys. Virus has now been isolated from mosquitoes caught in uninhabited forest in Bwamba country in W. Uganda, especially from *Aëdes tarsalis*, *A. albocephalus*, *Eretmopodites chrysogaster*, *E. normalis*, and *E. ferox*.

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* Formerly human immune serum was added, but cases of serum jaundice developed, some fatal, after an incubation period of 3–7 months. Possibly due to infective hepatitis or to some other icterogenic virus.

Pathology.—In man, unknown. In sheep, histological changes in liver similar to those of yellow fever.

Clinical features.—Incubation period, 4½–6 days : nausea, fullness in hepatic area, headaches, pain in back, flushed face, photophobia, furred tongue, epistaxis. Temperature 101–102° F. (38·5–39° C.) ; falls to normal on fourth day. Profuse sweats. Initial slight leucocytosis, then leucopenia.

Diagnosis.—Distinguished from yellow fever by milder course, and by pathogenicity for rats and mice on intraperitoneal injection.

Treatment.—Immune serum possibly of benefit. Glucose by mouth.

Prophylaxis.—Avoidance of infected sheep. Virus commonly conveyed by mosquito, *Mansonia fuscopennata.*

DENGUE

Dandy or Breakbone fever, Sellar fever ; a specific fever of short duration conveyed by bite of *Aëdes ægypti* and other closely related mosquitoes.

Geographical distribution and epidemiology.—In epidemics in Mediterranean (Greece, Syria, Turkey, Aegean), India, Malaya, China, Red Sea, Ceylon, Dutch E. Indies, N. Queensland, Pacific Islands, West Indies, Brazil and S. America. In South U.S.A. as far north as Charleston and Philadelphia. Recurs at interval of years. Epidemics may spread over several years. In pandemic form spreads beyond usual limits up to 5,000 ft. In north, extension occurs only in late summer and early autumn. Short immunity produced. Found usually in coastal areas, deltas and valleys of great rivers.

Ætiology.—Ultramicroscopic virus in blood can be preserved as in yellow fever. Conveyed by bite of *Aëdes ægypti* in which it undergoes development (possibly other species also : *A. albopictus* in Philippines; *A. tæniorhynchus* in Florida; *A. scutellaris*, *A. polynesiensis* and varieties in Pacific). Conveyed to volunteers by blood inoculation as well as by mosquito bite. Various species of monkey susceptible; one strain transmissible to mice by intracerebral inoculation (Sabin). In New Guinea jungle form of dengue recognized comparable to that of yellow fever. " Jungle " dengue is conveyed by *A. scutellaris*: urban in older established settlements by *A. ægypti.*

Pathology.—Few autopsy records. Localized pulmonary and intracranial inflammation ; periarticular effusions and involvement of crucial ligament of knee. Encephalitis recorded.

Clinical features.—Incubation period : 5–9 days. Fever : 3 stages as in yellow fever :

(1) Invasion, 2–3 days.
(2) Remission, 1–3 days.
(3) Reaction, terminal fever and eruption.

(1) *Invasion.*—Malaise; very severe rheumatic pains in leg, toe, fingers, knee joint. Commences suddenly; often rigor; deep flushing of face; photophobia; post-ocular pain, backache. Suffusion of face, mucous membrances, throat and eyes. *Tache cerebrale*=prodromal eruption. Prostration in few hours. Temperature 103° F. (39·3° C.)—105 or 106° F. rarely. Pulse 120. Skin hot and dry. Occasional vomiting.

(2) *Remission.*—Pain disappears; temperature normal 3–4 days. Tongue clears, appetite returns.

(3) *Terminal.*—Return of fever, slight, slight or severe, bone pains +. Rubeolar eruption lasts 3 days, followed by furfuraceous desquamation; absent in 25 per cent.; commences on palms and dorsum of hands, up arms back of chest and thighs; isolated, elevated, rubeolar spots, $\frac{1}{8}$–$\frac{1}{2}$ in., each surrounded by sound skin—" midway between measles and scarlet fever." Spots disappear on pressure, never petechial. Face seldom affected. Staining sometimes visible for 3 weeks. Bradycardia 40–50; + leucopenia (1,000–2,000 leucocytes); reduction of polymorphs (40 per cent.); relative increase of lymphocytes.

Convalescence.—Rheumatoid pains persist, may be permanent; periarthritis of knee; also in small muscles of hands, feet, and deep fascia. Anorexia, mental depression, insomnia, debility. Variability of type in different epidemics: some very severe, others short fever, no rash; great variability in epidemic types. In some swelling of joints and general adenitis. Urticarial and gastro-intestinal forms also recognized.

Immunity.—Not longer than 6 months. Repeated attacks common. Mortality nil.

Diagnosis.—Chief danger is confusion with typhus or some other severe fever. From yellow fever difficult in early stages. From measles, scarlet fever, influenza, hæmorrhagic smallpox, rheumatic fever or malaria, sandfly fever. Rash, bradycardia and leucopenia are characteristic.

Treatment.—Symptomatic; nursing in bed 10–14 days under mosquito net. Liquid diet. Diaphoretic mixture: *vinum colchici*, 15 min. (0·93 c.c.) t.d.s. Cold applications to head. Morphia $\frac{1}{6}$ gr. (10 mgm.) for pains. Urotropine mixture as routine.

Prophylaxis.—As for yellow fever. Measures directed against Aëdes with DDT.

COLORADO TICK FEVER AND BULLIS FEVER

The first is an epidemic disease in Colorado associated with the bite of the wood tick—*Dermacentor andersoni*. The virus is filterable and the clinical features resemble that of dengue. *Bullis or " Lone Star" Fever* is a new form described in soldiers in camp at Camp Bullis, near Houston, Texas, and is conveyed by multiple bites of the tick—*Amblyomma americanum*. The clinical features are similar with general adenopathy. It is possible that both these diseases may represent a tick-borne form of dengue.

PHLEBOTOMUS FEVER

Three-day fever. Sandfly fever. A short fever caused by virus introduced by bite of sandfly (*Phlebotomus*).

GEOGRAPHICAL DISTRIBUTION AND EPIDEMIOLOGY

A disease of sandy waste spaces, with a range co-extensive with that of the sandfly ; where absent, disease does not occur, *e.g.*, Bermuda. In the tropical zone may occur at any time ; in subtropics in summer and early autumn ; 75 per cent. of newcomers attacked ; indigenous natives immune. Mediterranean area, Greece, S. Italy, Middle East, Iraq, Caucasus, Central Asia, Chitral, N.W. India (to 4,000 ft.), S. China, Java, Brazil and N. Argentine.

ÆTIOLOGY

Ultramicroscopic filterable virus with same properties as that of dengue ; allied to, but distinct from, yellow fever. In blood for first and second day of disease ; can survive outside body 60 hours. Monkeys susceptible. Undergoes development in body of sandfly. No evidence of hereditary transmission through egg of sandfly, but larva is infected either by feeding on fæces of imago, or by eating dead adults. Recently proved in Russia that newly hatched female sandflies are infective. It must be emphasized that not all species of phlebotomus transmit the disease, only (as far as is known) in Europe, Middle East and Africa, *P. papatasii*; for there are many species of sandflies in Africa in localities where there is no sandfly fever.

Sandflies : *Phlebotomus*.—In Mediterranean *P. papatasii*. In most tropical and subtropical countries. Minute (1·5–2·5 mm.) greyish or brownish, slender insects ; females bite at night, males feed on organic matter ; can pass through meshes of mosquito net. Feeble powers of flight, range 50 yards. Wings folded roof-wise. Female lays about 40 eggs in rubble, cracks in masonry, etc. In 6–9 days caterpillar-like larva appears with two long dorsal bristles. Four instars with moults ; feeds on lizard fæces and carcases of adults ; pupa orchreous-buff. Stage lasts 9 days, whole cycle 7–8 weeks.

PATHOLOGY

No mortality ; pathological appearances unknown.

CLINICAL FEATURES

Incubation period 4–7 days. Sudden onset, severe rigor. Swollen, flushed face and injected conjunctiva (" dog-faced disease "—mastiff). Photophobia. Fauces congested, showing small vesicles. Severe frontal headache ; post-orbital pain ; stiffness and aching at back of neck ; influenza-like joint and bone pains ; epigastric pain. Band-like pain in lower thorax, prominent in recent epidemic in Palestine, reminiscent of epidemic pleurodynia (Bornholm disease). Blood : no anæmia ; leucopenia 3,000 first 4 days, then leucocytosis, 15–20,000 to 10th day. Drowsiness, insomnia. Bradycardia (40–55) on 2nd day. Temperature, 103–104° F. (39·5–40° C.) for 3 days ; then crisis ; normal on 4th or 5th day usually, but fever occasionally lasts up to 8 days. At crisis : epistaxis, vomiting, and sweating, diarrhœa. Serious cases resemble benign lymphocytic meningitis : head retraction, Kernig's sign, C.S.F. pressure increased, lymphocytes 74–300 per c.mm., albumin +, chlorides decreased. Debility during convalescence. Sequelæ : debility + ; acute sinusitis recently observed.

DIAGNOSIS

On clinical grounds. Slight fever with no rash. Very often simulated by mild subtertian malaria; also from dengue, paratyphoid, typhus, influenza.

TREATMENT

No specific ; *Tinct. opii*, min. 30 (1·8 c.c.), relieves headache. Tinct. iod. to sandfly bites. Stiffness of neck relieved by lumbar puncture.

Prophylaxis.—Measures against sandfly. DDT is deadly to sandflies in the adult stages. Burn rubbish, demolish ruined walls, bury rubble, fill cracks with tar ; fumigate latrines with sulphur. Kill adult sandflies by "swatting" ; sandfly nets impracticable. Camphor on bed and dibutyl phthalate on hands and face repel sandflies.

In Army, shorts should not be worn after sundown. Wellington boots for legs and ankles. Electric fans in barracks and dormitories create upward draught and blow away sandflies—most effective.

PSITTACOSIS (ORNITHOSIS)

Originally disease of parrots (especially S. American) communicable to man now found in other birds, budgerigars, pigeons, etc.

GEOGRAPHICAL DISTRIBUTION AND EPIDEMIOLOGY

Outbreaks in England, France, Germany, Switzerland, U.S.A., California, and probably Brazil, S. America, Australia. Similar disease now in Faroe Island and Iceland conveyed by fulmar petrel (*Fulmarus glacialis*). Pigeons, ducks, gulls, finches, thrushes and waders (willets) also found infected. Not epizoötic under natural conditions, but only in parrots in captivity in insanitary conditions. In budgerigars especially in cold weather. Parrots remain in subacute infectious state for years. Human infection usually directly from parrot, but transference of virus from man to man recorded.

ÆTIOLOGY

Ultramicroscopic virus (particles 220–235 mμ) in blood up to 10th day. Other birds—hens, canaries, finches, thrushes—susceptible ; also guinea-pigs and rabbits ; mice by intraperitoneal injection ; intracerebral injection causes encephalitis. Virus bodies stained by Giemsa visible in tissues of diseased parrots and in man.

PATHOLOGY

In parrot: pericarditis with hæmorrhages. Liver studded with white necrotic foci.

In man: septicæmia with distinctive inflammation of lungs—hæmorrhagic, vesicular pneumonia, pulmonary thrombosis and mucopurulent bronchitis. Spleen enlarged, diffluent. Cerebral purpura.

CLINICAL FEATURES

Incubation period: 8–10 (occasionally 16) days. Severe illness for 2–3 weeks. High pyrexia for 7 days. Rigors occasionally. Epistaxis, bone and muscle pains; then typhoidal, with paroxysmal cough, scattered lung consolidations, constipation, abdominal discomfort, and semi-coma with muttering delirium. Then fall by lysis and improvement in 3 days. Mild ambulatory cases reported, with sore throat, peribuccal œdema and often epistaxis. Relative bradycardia. Photophobia. In some cases " rose spots " on chest and abdomen, 2–4 mm., fading on pressure 7–13th day. No characteristic blood picture. Protracted convalescence with liability to femoral thrombosis. Mortality, 20 per cent.

DIAGNOSIS

Not easy; many features resemble typhoid, also influenza. Inoculation of blood and sputum fatal to mice. Complement fixation reaction (Bedson)—antigen from spleen of infected mice—is most certain method of diagnosis. Pacheco's parrot disease similar, but not communicable to mice or man.

TREATMENT

Symptomatic; similar to typhoid. Penicillin, chloramphenicol and aureomycetin all effective.

Prophylaxis.—Prohibition of importation of diseased parrots, especially from S. America. Difficult in California where birds (budgerigars and paroquets) may be infected and show no signs of disease.

EPIDEMIC HÆMORRHAGIC FEVER (RED FEVER OF KOREA)

Resembles " scrub typhus " in epidemiology. Although known to Russians and Japanese, only became familiar to Western Medicine in the Korean War (1952, 1953). Cause is not exactly known, but is generally thought to be a virus, transmitted to man by a mite (*Lælaps jettmari*) and that the reservoir is a field-mouse (*Apodemus agrarius*).

Pathology.—General vascular collapse. Kidneys resemble acute glomerular nephritis albuminuria, mononuclear cells and renal tubular cells. Kidneys: cortex sharply demarcated from medulla. Hæmorrhages present.

Clinical features.—Seasonal incidence. Most frequent in May, June, October and November. Fever lasts 7 days, recovery in 14. Fatality rate about 13 per cent. Fever, myalgia, albuminuria and petechial rash. In severe cases hæmoptysis, hæmatemesis, hæmaturia and melæna; onset abrupt. Conjunctival ecchymosies frequent. Photophobia and œdema of upper lids, intense toxic erythematous blush of face and neck. Death due to peripheral vascular collapse.

Urine.—Albuminuria 28–72 hours from onset, persists for one week. Specific gravity 1005, albumin 1–4 per cent.

Treatment.—Symptomatic only. Antibiotics and sulphonamides useless. Fluids in small amounts on account of increased capillary permeability.

IZUMI FEVER

Found only in Japan since 1927, resembling scarlatina. Outbreak in Sakishima district south of Tokyo in 1951. Occurs sporadically and in epidemics. Characterized by rash, temperature chart and gastro-intestinal upsets. Severe and mild forms recognized. Incubation period 5–13 days. Onset abrupt with a temperature of 103–104° F. (39·5 40° C.). Joint pains and lumbar pains, vomiting and anorexia. Rash in first and second days with itching. Slightly elevated papules on flushed skin, lasting 3–4 days, on trunk, face, neck and extremities. Usually after interval of 2 days rise of temperature with a secondary rash. Then periods of sweating with gradual remitting fever for 4–5 weeks. Desquamation on 10th day completed in fourth or fifth weeks. Hepatomegaly noted in one third. Evidence, on epidemiological grounds, that field-mice (*Apodemus speciosus*) may be reservoir of virus. Treatment with aureomycin satisfactory.

OTHER VIRUS DISEASES WHICH HAVE BEEN DESCRIBED

Durand's virus (D) pathogenic for man and guinea-pig. Mice easily infected. Cultured on chorio-allantoic membrane of chick.

Bwamba fever in W. Uganda. Five-day fever of sudden onset. Pathogenic for mice. *West Nile virus* widely distributed in West Nile area, Sudan, Uganda, Kenya, Congo. Immune bodies in blood of forest monkeys *Cercocebus* and *Colobus*.

Meningo-encephalomyelitis in Uganda causes paralysis in man and monkeys and is known as Semliki virus and is found in mosquitoes. Other viruses isolated from mosquitoes *Aëdes* and *Psorophora*, known as Uganda S., Bunjamwera, Ntaya and Zika.

Salisbury fever affects children of 4–9. Acute type of fever (T. 104° F.) lasting 3–14 days. General lymphadenitis with splenomegaly. Relapses frequent.

POCK DISEASES

SMALLPOX

Severe smallpox now confined to tropics and subtropics. Severe outbreaks in India, China and Nigeria.

Ætiology.—Vaccinia now regarded as original virus. Variola virus converted into attenuated form by inoculation of monkeys and then intratesticularly into rabbits ; indistinguishable from vaccinia (cowpox). This transition is not reversible. Virus : spherical

(0·17 μ), "Paschen body." Pure suspensions now obtained; contain phosphatase and catalase. Bodies exceptionally sensitive to flocculation by salts. Readily visible under dark-ground illumination. Inoculated into skin, elementary bodies penetrate cytoplasm of epidermal cells, increase in number and show acidophilic inclusions (Guarnieri bodies). Virus in cells causes hypertrophy and produces papule. Later, degeneration and liquefaction produce vesicle, which is then converted into pustule by immigration of polymorph cells. Fluid forms culture medium for staphylococci and other organisms. Crusts or scabs on pustule contain active virus. High infectivity of smallpox probably due to lesions in mouth, throat and lungs; expressed air contains elementary bodies; air breathed by susceptible persons causes infection.

Vaccinia and variola cultivated, as other viruses, in presence of living cells in tissue culture of rabbit testes, corneal epithelium and in fluid medium of rabbit's serum and Tyrode's solution with minced rabbit kidney. Also on chorio-allantoic membrane of chick embryo. Culture virus inoculated by scarification.

Diagnosis.—Elementary virus bodies readily demonstrated in vesicle fluid by dark-ground illumination; also stained by Gutstein's method: (1) 1 per cent. methyl violet, (2) 2 per cent. $NaHCO_3$. Dry films in air, rinse with normal saline and distilled water, dry, fix in methyl alcohol for half an hour, mix equal parts 1 and 2 in test tube, filter on to slide, cover and incubuate at 37° C. for 30 minutes, rinse in distilled water and mount in cedarwood oil. Elementary bodies stained voilet. Of no value in differentiating between smallpox and chickenpox.

Serological diagnosis.—Pocks lightly scraped with scalpel, material suspended in saline, clarified by centrifugation, then mixed with dilutions of rabbit anti-vaccinial serum, tubes incubated at 37° C. Positive reaction: finely floccular precipitate. Reaction specific for variola and vaccinia. Serum of patient in second week of disease gives similar reaction. No antigenic difference between true smallpox and parasmallpox.

Treatment.—Virulence of smallpox largely due to secondary pyogenic infection of respiratory tract; now treated with sulphapyridine, 3–4 gm., daily and application of sulphonamide paste to pustules. Treatment of smallpox by potent antivaccinia serum under trial. Penicillin indicated in pustular stage when infected with penicillin-sensitive strepto- or staphylococci.

ALASTRIM. AMAAS. PARASMALLPOX

Modified smallpox occurring in outbreaks.

Geographical distribution and epidemiology.—West Indies, Brazil, Central and South America, Mediterranean, Great Britain. Especially in Trinidad. Differs from smallpox in rate of spread; smoulders, never assuming features of large epidemic. Spreads by contact and overcrowding.

Ætiology.—As for smallpox; vaccination protective in high degree.

Clinical features.—Incubation period, 14 days. Initial stages resemble influenza and are often mistaken for it. Seldom shows the severe headache, vomiting and rigors typical of smallpox. Eruption, 3rd–4th day, on buccal mucosa and on skin, extends from palate into bronchi. Involvement of skin intermediate between chicken-pox and smallpox. Papules palpated beneath skin. Eruption in one crop, papules umbilicated, crusting at end of first week, and have fallen at end of second or third. Distribution centrifugal. Protected parts (axillæ, groins, abdomen) free. Face, scalp, shoulders, back, arms, legs most affected. Pocks cluster at site of old scars ; confluent rashes rare. Prodromal rash absent. Mortality rate 0·45 per cent.

Treatment.—Symptomatic only ; isolation.

Prophylaxis.—Vaccination most efficient against spread.

RABIES (Hydrophobia)

A disease of the C.N.S. in dogs and other animals, transmitted to man and animals by inoculation of saliva.

GEOGRAPHICAL DISTRIBUTION

All over world, in Greenland, Iceland and Far North. Has disappeared from England ; less prevalent than formerly in most European countries ; common in tropics and subtropics in virulent form, wherever wild dogs, wolves and jackals are common. In W. Indies and S. America, paralytic rabies is transmitted by vampire (*Desmodus*) as well as by insectivorous and fruit-eating species (*Dasypterus, Lasiurus, Phyllostoma* and *Artibeus*).

All warm-blooded animals susceptible if subjected to bites of foxes, jackals, wolves, dogs ; also skunks, weasels, stoats, mongoose and rats ; in S. Africa, meer cat ; in North U.S.A., grey squirrel. Donkeys refractory; dogs, camels, cattle, horses, pigs, cats, sheep, goats, susceptible.

ÆTIOLOGY

Ultramicroscopic, filterable virus, propagates in nerve endings in neighbourhood of bite. Travels up nerve sheaths to C.N.S. ; primary stimulation, then destruction.

Street virus.—Virus in nervous tissue in naturally-transmitted disease. Virulence variable when inoculated subdermally into rabbits.

Fixed virus.—Obtained from street virus by passage through long series of rabbits ; fixed incubation period, constant results. One to four Negri bodies in 100 ganglion cells of ammon horn.

Negri bodies.—Oxyphilic granules in ganglion cells, probably same as cytoplasmic inclusions in ammon horn (hippocampus major) ; used for diagnosis ; not present in every case, only when disease well developed. Therefore dogs should not be killed on suspicion, but kept till bodies have probably developed.

Location of virus.—C.N.S. and peripheral nerves ; infectiousnes, variable. Medulla five times more virulent. Salivary glands of infected dogs constantly infectious, but not blood, fœtus, milks urine, liver or spleen.

Cultivation.—Difficult ; obtained in plasma medium, in minced chicken embryo and in Tyrode medium.

Physical properties.—Size 100–150 mμ, obtained by centrifugation and concentration ; heat sensitive when moist ; in dried form resists 105° C. for 2 minutes ; can resist intense cold and glycerine (50 per cent.) for months. Sensitive to acids and alkalis.

Trinidad disease ("Paralyssa").—Paralytic form in cattle and man—transmitted to monkeys. Vector : saliva of local species of vampire bat (*Desmodus rotundus*).

CLINICAL FEATURES

Incubation period : long and variable, seldom 10 days, may be one year, usually 3 months. Longer in man than in animals, depends on site of bite (proximity to brain), severity of wound and physical condition of patient.

Two types : (*a*) furious—excited ; (*b*) dumb—paralytic.

(*a*) **Furious.**—Rapid onset ; insomnia, twitchings +, pyrexia. *Hydrophobia:* painful spasms of œsophagus ; sight and smell of liquid precipitate attack, superficial and deep reflexes exaggerated, mind clear, bouts of mania, sexual excitement, priapism, hoarse voice, expectoration, noise like bark of dog. Convulsive seizures, ropy saliva, dilatation of pupils, respiratory paralysis. Average duration, 3½ days.

(*b*) **Dumb.**—Paralytic, often unrecognized ; infection with large amount of virus, involvement of spinal cord. Pyrexia malaise, headache, vomiting, pain in site of bite, numbness, ataxia ; girdle pains ; consciousness retained, creeping Landry-type paralysis of limbs, trunk, bladder, face, tongue and ocular muscles. Death from respiratory paralysis. *No hydrophobia.* More prolonged than (*a*) ; lasts 7½ days.

Paralytic type most frequent in animals ; in dogs : wavering gait, drooping of ears, complete paralysis, chew sticks and stones, swallowing impossible. Rabid type : marked changes in disposition, morose, sullen, irritable ; growls, barks, bites, laps water, but unable to swallow, convulsions, death.

Immunity.—In lower vertebrates ; rare in man. Acquired immunity by inoculation of modified form of rabies virus. Virus most virulent for rabbits and after inoculation loses virulence for higher animals. Spinal cord of rabbit dried gradually loses infective power. Unattenuated *fixed virus* now used for production of immunity ; no danger of rabic infection.

DIAGNOSIS

History. Chief difficulty is simulation by hysteria ; hypersensitiveness to draughts of air suggestive. May simulate tetanus and mania. Paralytic rabies resembles Landry's paralysis. In dogs, distemper, dog hysteria or brain tumours simulate rabies.

Pseudo-rabies, "mad itch."—Virus affects ganglia and produces intense itching. Non-fatal disease ; has been communicated to man. "Psychological rabies" recorded in doctors and veterinarians.

TREATMENT

No special treatment ; symptomatic. Chloroform inhalations for spasms ; chloral and bromide *per rectum* and, if possible, curare subcutaneously. Morphia increases mental excitement and suffering. Rectal nutrient enemata when swallowing impossible.

Prophylactic inoculation of those exposed to infection.—Cauterization of wound probably prolongs incubation period and allows time to establish immunity by antirabic inoculation.

Preventive inoculation.—Production of immunity is long process, but incubation period of rabies is normally longer. Modification of rabies virus by several passages through rabbits ; subsequent attenuation of toxicity by desiccation. Modern opinion is inclined to the injection of hyperimmune serum to reinforce vaccine treatment. The following methods are employed:—

(1) Unmodified fixed virus. (2) Dilution of fresh fixed virus. (3) Fixed virus attenuated by desiccation—original method of Pasteur—dried virus preserved in glycerine. In first 4 days, two 3-c.c. injections made daily of dried cord (dried *in vacuo*, 14, 13, 12, 11, 10, 9, 8, 7 days). Treatment for 21 days. (4) Carbolized fixed virus used in India ; whole brain in solution of 1 per cent. phenol in 0·85 per cent. saline, mixed in mortar at 37° C. for 24 hours. Suspension stored at 0° C. (32° F.). Essential inoculation contains 0·5 per cent. brain substance. Dose 4 c.c. daily for 14 days. Mass vaccination of dogs with chick-embryo vaccine in Israel and Malaya is now being undertaken with success. The efficacy of both living and killed vaccines has been amply demonstrated. *Per se* canine vaccination alone cannot abolish rabies. It can have no effect on other animals which really constitute the reservoir of the disease.

Indications for treatment.—All who have been bitten and who have open wounds, scratches, etc. If animal is alive and *well* for 10 days, treatment may be discontinued.

Examination of suspected material.—Head of suspected dog or other animal, wrapped in cloth soaked in bichloride of mercury. For inoculation, place medulla in glycerine. Sections give better result than smears. Smears and sections made from hippocampus major are fixed and stained with Unna's polychrome methylene blue for 3 minutes and differentiated in 95 per cent. alcohol. Negri bodies stain magenta colour.

LYMPHOGRANULOMA INGUINALE (L.I.)

L. venereum. Lymphopathia venereum. Climatic bubo.

A venereal disease accompanied by suppuration of the lymphatic glands, produced by filterable ultramicroscopic virus.

GEOGRAPHICAL DISTRIBUTION AND EPIDEMIOLOGY

Very widespread in tropics and subroptics, increasingly so in Europe, France, Germany, England. Especially in E. and W. Africa, India, China, Malaya, Japan, E. Mediterranean, W. Indies and S. America and U.S.A. Rediscovered in France as "Nicolas Favre disease." Infection mostly contracted by Europeans from native women.

ÆTIOLOGY

Pus inoculated intracerebrally produces meningo-encephalitis in monkeys ; virus particles contained in leucocytes ; visible if stained by Giemsa or Castañeda stain ; also within cells in groups or clusters. Developmental cycle of virus particles completed in 48 hours. Size, 125–175 $m\mu$; resemble bodies found in psittacosis. Intraglandular injection into guinea-pigs produces inguinal bubo ; intracerebral injection into mice, encephalitis ; also intratesticular and intracerebral inoculation of chipmunks. Cultured in tissue culture and in chorio-allantoic membrane of chick. From non-ulcerative proctitis by insertion of tissue removed by biopsy under skin of guinea-pig and reproduction of buboes.

Protection test.—Equal parts of serum of patient and mouse brain emulsion 1 : 5 in normal saline kept at 4° C. (39·2° F.) and 0·5 c.c. injected intracerebrally : does not produce encephalitis in mice.

PATHOLOGY

Pin-point epithelioid formation and eventually abscesses scattered throughout substance of lymphatic glands. Irregularly-disposed histiocytes and giant cells ; sometimes eosinophiles.

CLINICAL FEATURES

Small herpetiform ulcer on prepuce in males heals in few days ; secondary adenitis. Not seen in circumcised. In female : typical inguinal periadenitis uncommon owing to anatomical arrangement of lymphatic glands. Esthiomène and rectal stricture associated with infection—*genito-ano-rectal syndrome*. Ulceration of vulva with elephantiasis of labia. Primary lesion in posterior vaginal wall ; ano-rectal lymphatic glands affected ; then spreads *via* lymphatics to anterior vaginal wall and posteriorly to rectum. Scarring of glands leads to rectal stricture ; non-malignant stricture of rectum invariably due to L.I., not to syphilis. More frequent in Europeans than in natives. Eighty per cent. give positive Frei-Hoffmann intradermal test (*q.v*). Extragenital infections : on tongue with lymphadenitis of cervical glands, in axilla, and on foot.

Incubation period : 3–4 weeks to 2 months. Pyrexia of remittent type may precede localizing signs. Subacute inflammation of groin glands—unilateral or bilateral—oblique glands first, then crural, also internal iliac and lumbar. Toxæmia from absorption ; infected glands may suppurate or may subside. Periglandular inflammation. Fistulæ discharge clear, gummy serum. If excised, heal, but may be followed by elephantiasis of leg or scrotum, or secondary sepsis. Rheumatic painful effusions into knee and other joints noted ; suppuration may rupture into bladder.

Rectal stricture in man probably due to introducing virus into rectum ; at first causes ulcerative proctitis with blood and mucus stools. Anal stricture more common in women, associated with esthiomène; annular and tubular strictures recognized and may be associated with carcinoma; most severe are rectal communicating strictures between bladder and vagina in female, and between bladder, prostate and seminal vesicles in male.

DIAGNOSIS

From clinical appearances. **Intradermal Frei-Hoffmann reaction.** Pus from aspirated gland mixed with sterile saline (1 : 5) heated to 60° C. (140° F.) over waterbath, kept at low temperature and protected from light. Potency preserved for three months. Also from excised gland. 0·1 c.c. antigen introduced intradermally on forearm : wheal (8–10 mm.) ; control with normal saline and Dmelcos chancroid antigen. A hard mass of indurated skin persists for few days. Antigen now also prepared from encephalitic mouse brain, injected intracerebrally with virus (Findlay) ; more satisfactory. Usually leucocytosis 27,000.

Wassén test : fatal encephalitis in mice by inoculation of virus.

Biopsy test : demonstration of pin-point epithelioid formations and giant cells.

Complement fixation : unsatisfactory.

Differential diagnosis.—Bubonic plague, filarial adenitis, soft sore, streptococcal abscess, tularæmia, lymphadenoma and femoral hernia.

TREATMENT

1. When discrete, surgical excision is rapid and safe. Incision contra-indicated ; usually leads to secondary sepsis and formation of intractable sinus.

2. Protein shock therapy effective when suppuration has commenced, combined with aseptic aspiration. T.A.B., 50–300 million organisms intravenously : 2–3 reactions produced and disappearance of lesions. In chronic suppuration : application of *unguentum hydrarg*.

3. Intravenous tartar emetic, 15 injections of 5–10 c.c. of 1 per cent. solution. Pentavalent antimony compounds perhaps better, but results uncertain.

4. *Sulphonamides.*—Sulphapyridine (M. & B. 693), 1·5 gm. (23 gr.) daily ; increase to limit of tolerance ; average dose in U.S.A. 98 gm. (1509 gr.) over 34 days. Effect on virus (experimental evidence in mice) now generally accepted.

5. Chloromycetin and aureomycin are now claimed superior to any other form of treatment in generally accepted dosage (Smadel).

Rectal stricture.—May simulate ulcerative colitis. In women with leucorrhœa and vaginal ulceration with proctitis, sulphonamides —especially sulphapyridine—efficacious. Dosage large : total, 100 gm. (1540 gr.) in two courses of 15 days. Treatment of fibrous rectal stricture more difficult ; in early stages, excision ; later, complete proctectomy and possibly colostomy. Diathermic dilatation also employed.

ENCEPHALITIS JAPONICA

Type B encephalitis.—An epidemic encephalitis involving brain and spinal cord ; occurs in waves in Japan and Okinawa ; differentiated from encephalitis lethargica ; spreads rapidly like poliomyelitis.

Ætiology.—Virus isolated ; monkeys and white mice susceptible. Active in blood and C.N.S. in early stages ; neutralized by convalescent serum. Transference to man not ascertained : possibly (as in equine encephalomyelitis) by mosquitoes.

Pathology.—Diffuse lesions in brain and cord, aggregations of neuroglia, round cells, ganglia cells damaged.

Clinical features.—Prodromata : dizziness, sluggishness, vomiting ; then physical disturbance, delusions, coma, death.

In contrast to *Encephalitis lethargica*, meningeal symptoms predominate ; motor disturbances, chronic muscle contractions and athetoid movements, especially of face. Trismus +. Eye symptoms absent. Bulbar symptoms : failure of speech and deglutition. Strabismus and Kernig's sign present. Leucocytosis 60,000–88,000 with high proportion of polymorphs and secondary anæmia. Generally febrile, but fulminating cases pyrexial.

Diagnosis.—Differentiation from encephalitis lethargica. C.S.F. shows all grades of inflammatory disturbance.

TICK-BORNE ENCEPHALITIS

In Mongolia and Far East (Taiga country), discovered by Pawlowsky and colleagues. In general appearance resembles E. japonica. Due to filterable virus transmitted by bite of tick (*Ixodes persulcatus*) which is infected with virus in unpopulated districts. Virus, distinct from other forms of encephalitis, recovered from brain of several species of indigenous mammals which constitute reservoir. Distinct characteristic seasonal incidence—80 per cent. of cases in May and June—follows on period of maximal activity of this species of tick, which can carry disease in all stages from larva to adult. Infection hereditary in tick.

Pathology.—Resembles E. japonica and St. Louis' encephalitis. Histologically : meningo-encephalitis. Virus neutrotropic, infective to rodents, monkeys and birds ; white mice specially susceptible.

Clinical.—Meningeal involvement followed by signs of focal lesions of C.N.S., paresis and paralysis of lower limbs, neck and back muscles. Parkinsonism never. Case mortality : 40 per cent.

Treatment.—Antiserum prepared ; said to be effective.

Prophylaxis.—Prophylactic inoculation from bodies of ticks under preparation in E. Russia.

MURRAY VALLEY ENCEPHALITIS

Probably identical with Japanese *B. encephalitis.*

S. Rhodesian encephalitis is due to the Coxsackie B virus of Bornholm disease, associated with myalgia and other symptoms of that disease. Virus isolated from fæces. Clinical appearances those of a typical meningo-encephalitis.

CHAPTER VI

FUNGOUS DISEASES

MYCETOMA (MADURA FOOT)

Tropical fungous disease of the foot, rarely of hand and internal organs.

Geographical distribution and epidemiology.—Widespread in India in rural districts. Senegal, Morocco, Algiers, Egypt, Sudan, Somaliland, Aden, Madagascar, Cochin China, South U.S.A., S. America. Occasional cases described in E. Mediterranean and S. Italy. Never in towns ; always in field-workers.

Ætiology.—Various species of actinomycosis described :—

Two main forms of maduromycetoma, as distinct from actinomycetoma, described. Black-grained mycetoma—*Madurella mycetomi*—is the common infection with black grains in Tropical Africa, India and other Asiatic countries and parts of N. and S. America.

The grains of *M. mycetomi* radially-spreading, septate, branching mycelium (1–5 μ diameter) with chlamydospores up to 25 μ in diameter. *M. grisea* is mainly found in S. America. In this form the central part is unpigmented surrounded by black cortical zone. In the marginal zone the mycelium is embedded in a brown cement. Cultural characteristics of these two species permament on Sabouraud's medium. The yellow-grained fungus is *Nocardia somaliensis* and the red-grained is *N. pelletieri* (or *Streptomyces somaliensis* and *S. pelletieri*).

Pathology.—Section of mycetomatous foot, express oily surface ; anatomical elements unrecognizable in pale yellow mass. Disappearance of bones, network of sinuses and cysts. In black variety material is black or dark brown. In white, it is a white or yellow roe-like substance containing mycotic elements.

Clinical features.—Commences on sole of foot, usually at site of trauma, as small, firm, rounded, painless swelling (½ in. diameter). Ruptures, discharges oily, purulent, bloodstained discharge containing " sulphur grains " (in black varieties " gun-powder "). Sinuses form, general increase of bulk of foot, retraction of toes. Surface of skin roughened and corrugated. Profuse discharge. Leg atrophies from disuse. May extend to tibia; occasionally forearm, rarely knee, thigh, jaw, scalp or testicle or lachrymal glands. Purulent mucoid fluid exudes containing characteristic grains of the fungus. Sinuses develop. Regional glands enlarged and infected. No fever or other systemic effects.

Treatment.—In advanced cases amputation well above seat of disease. *Tincture of iodine* 1–2 c.c. injected into any suspicious area every 10 days for 2 months. Potassium iodide by the mouth in large doses. More recently sulphonamides—sulphapyridine and sulphathiazole—in full doses combined with penicillin 1½–2 mega units.

BLASTOMYCOSIS

Lesions produced by yeast-like fungi in tissues.

COCCIDIOIDOMYCOSIS is a common disease in S.W. U.S.A., in California, Texas, Arizona and New Mexico. *Coccidioides immitis* may produce benign, self-limited respiratory disease, or progressive, chronic disseminated disease, involving cutaneous, visceral and osseous tissues.

(1) In the primary form " S. Joaquin Valley or Desert Fever " organisms inhaled with dust produce pneumonic type of infiltration accompanied by erythema multiforme, erythema nodosum and high eosinophilia. Radiography shows nodular lesions in lung parenchyma.

(2) Non-pulmonary primary coccidioidomycosis occurs on exposed surfaces (Posada's disease), commences as small pink nodule which subsequently ulcerates. May become generalized and resemble progressive tuberculosis.

COCCIDIOIDAL GRANULOMA.—Verrucose or ulcerative skin lesions, sometimes with involvement of bones, joints, viscera. Skin lesions : nodular, ulcerated, papillomatous or verrucose, resembling tuberculosis. Fungous elements, isolated, or in giant cells.

Coccidioides immitis.—Cysts (4–80 μ) with endospores and thick double-contoured capsule. Culture : creamy-white colonies, 4–17 days, on malt-extract agar. Later chlamydospores and hyphæ. Lesions produced in laboratory animals. Four hundred cases in U.S.A., mostly in S. and W. (80 per cent. in California). " Valley fever " or " desert fever " of San Joaquin Valley resembles erythema nodosum with pulmonary involvement. Generalized infection may ensue by inhalation of chlamydospores.

Differentiation.—From tuberculosis, syphilis, erythema multiforme, e. nodosum, and other fungous infections.

Treatment.—Intravenous injections of stilbamidine now claimed effective in all forms of blastomycosis. *Nystatin* (mycostatin or fungicidin) fungistatic antibiotic, now undergoing clinical trials.

OTHER FORMS OF BLASTOMYCOSIS.

N. American Blastomycosis or Gilchrist's disease (*Blastomyces dermatitidis*) :—Infectious verrucose or gummatous granuloma of skin. Organism: simple budding yeast-like cells, septate hyphæ on culture. European blastomycosis (*Cryptococcus hominis*) clinically similar ; cutaneous form with abscesses ; may invade C.N.S.

South American Blastomycosis (Lutz-Splendore de Almeida Disease) (*B. brasiliensis*) confined to S. America. Fungus differentiated culturally and produces visceral lesions.

Chromoblastomycosis, S. American form, also in South U.S.A, S. and E. Africa—*Phialophora verrucosa* (*P. pedrosoi*).—Diffuse nodules resembling barnacles in skin without involvement of internal organs. Cells spherical or ovoid, 1–30 μ, with thick walls, said to be saprophytic on plants. Produces condition known as "Mossy Foot."

Torulosis.—*Torulopsis histolytica* (*Cryptococcus histolyticus*).—Primitive yeast, multiplies by gemmation, easily cultured on broth. No endospores or mycelium. Definite affinities for C.N.S. and lungs. Enters by respiratory tract. Brain: tubercle-like lesions; choked discs suggest brain tumour. Diagnosis by yeast-like cells in C.S.F.

Sporotrichosis in S. France, South U.S.A., S. America, S. Africa.—Gummatous, circumscribed swellings of limbs and trunk.

Sporotrichum beurmanni, or *S. schencki*.—Cigar-shaped yeast bodies, phagocytosed in monocytes, scanty in pus. *Culture* (essential) on maltose agar. Does not produce mycelium or endospores, but hyphæ and chlamydospores. Linear nodules on arm; usually resemble tuberculosis. Occasionally pulmonary lesions. *S. beurmanni* is common parasite on plants—"bud-rot" on carnations. *S. schencki* is virulent for animals, but rarely fatal in man; pot. iod. effective in large doses.

Hemisporosis (*Hemispora stellata*), number of cases from S. Italy, like sporotrichosis. Granulomatous growths like T.B. or syphillis. Bones occasionally affected.

Histoplasmosis (*Cryptococcus capsulatus*, formerly *Histoplasma capsulatum*) in man and dogs resembles *C. farciminosus* of the horse, produces disease like kala-azar with hepato- and splenomegaly. Probably commoner than formerly thought in U.S.A., Panama and England. Parasite of reticulo-endothelium, found in epithelioid cells of lungs. *C. capsulatus* is an oval, apiculate yeast. Culture: ground-up tissue or pus-like lesions sown on trypsinized serum, copper sulphate agar at 24° C.; produces mycelium and tuberculated chlamydospores; yeast forms develop at 37° C.; reproduce by budding. Man probably acquires infection from dogs.

Clinical features.—Produces chronic pyrexial illness, cough, anæmia, asthenia. Hepatomegaly invariably present, but spleen not always enlarged. Pulmonary invasion occurs as part of generalised disease. Radiography reveals enlarged hilar glands, with peribronchial thickening and sometimes with nodules. In U.S.A. common, liable to be mistaken for tuberculosis. Differentiated by *histoplasmin* test, obtained from suspensions of yeast form of fungus in broth. Intradermal reaction similar to that of tuberculin. In Rio de Janeiro 16·4 per cent. react to histoplasmin and 89 per cent. to tuberculin.

Lingua nigra.—*Cryptococcus linguæpilosæ*, yeast-like organism with double-contour oval cells; mycelial elements cultured on glucose agar. Produces "black tongue," characteristic black or brown elongated papillæ, like black hairs; deep ulceration of buccal mucosa and throat. Recently reputed to be cured by nicotinic acid, 150 mg. daily.

FUNGOUS SKIN DISEASES

DHOBIE'S ITCH (*Tinea cruris*).—Itching ringworm of skin in crutch or axilla. Causative fungi are, in modern terminology:—*Epidermophyton floccosum* (syn. *E. cruris*, *E. inguinale*), *Trichophyton mentagrophytes* (syn. *T. gypseum asteroides*), *T. rubrum* (syn. *T. purpureum*) and *Nocardia minutissima* of erythrasma. *E. floccosum* peculiar to man. *T. discoides* is the cattle ringworm which may affect man. Easily cultivated on Sabouraud's agar medium—slowly. Subcultures tend to be cotton-like and show fewer spindles.

Clinical features.—In damp, hot weather produces painful dermatitis; commences as small, rounded, elongated papules with festooned edge causing excessive irritation in crutch and axilla; may extend from crutch into perineum and natal cleft. In women found on skin under breasts and forms patches resembling tinea circinata. In cool weather affected parts are dry, pigmented and scurfy, fungus quiescent.

Diagnosis.—Clinical appearances; scales removed and soaked in *liq. potassæ* show mycelium. Differentiate from seborrhœic dermatitis, intertrigo and flexural psoriasis.

Treatment.—Wear linen shorts, changed daily. Wash thoroughly with soap and water; preliminary treatment with lead lotion allays irritation. In thick-skinned natives, linimentum iodi., double strength, is effective but is too irritating for Europeans. Tincture of merthiolate (Eli Lilly & Co.) painted daily is effective, also cignolin (refined chrysophanic acid). Mixture of Cadogel (proprietary tar preparation): 1 gm. (15·4 gr.); cignolin 0·2 gm. (3 gr.), benzol 10 gm. (154 gr.); paint on affected areas twice daily and cover with strips of gauze. *Mycozol* consists of acid salicyl 4 per cent., chloretone 5 per cent., and mercury salicylate 4 per cent. in a mixture of lanolene and vaseline.

Prophylaxis.—Change underlinen daily, powder axilla and crutch with equal parts boric acid, zinc oxide and starch or merthiolate powder (Eli Lilly & Co.).

Pityriasis versicolor (*Tinea versicolor*) common in coloured people. Causes pale, slightly scurfy patches on chest and back. Common in young adults, favoured by excessive sweating. Several fungi involved—*Malassezia furfur* and *Cladosporium mansoni* which produces black hemispherical colonies on maltose-agar and black patches on affected skin. Mycelium and spores refractile, with hyphæ 2–3 μ and spores 3–8 μ. Fluorescence demonstrated by Wood's light. Difficult to culture from scales on account of secondary infection.

Erythrasma a chronic fungous infection of stratum corneum caused by *Nocardia minutissima* and producing superficial lesions in axilla, crutch and other intertriginous areas common in tropics. In skin scrapings fungus is short delicate branching filaments 1 μ or less in diameter.

Treatment as above.

TINEA IMBRICATA. TOKELAU RINGWORM.—Widespread in natives of S. Pacific, Burma, Formosa, S. China, Central Africa, Brazil. Requires damp, equable climate, 80–90° F. (27–32·5° C.). Fungus : *Epidermophyton concentricum* and *E. indicum;* mycelium cultured by soaking scales in alcohol (5 minutes), in glucose broth and then in Sabouraud's medium. Scaly limpet-like growth in 3–4 weeks. Demonstrated in scales with *liq. potassæ*, stained by carbol-gentian violet. Branching mycelium between epidermis and rete malpighii produces concentric scaling.

Clinical features.—At first confined to one or two spots ; soon occupies large area and sweeps over whole body, with exception of palms, soles, crutch, axillæ and scalp. In a year large part of body covered with dry tissue-paper scales in concentric parallel lines ; arrangement characteristic, largest scales usually between shoulders. Itching +. Distinguished from other mycoses by absence of inflammation and by characteristic concentric appearance.

Treatment.—Application of *lin. iodi*, or chrysophanic acid (20 gr. to ounce) ointment. Not found in natives who oil skin with coconut oil.

RINGWORM OF FEET.

Hongkong foot, Mangoe Toe—*Tinea pedis.* Originally confined to tropics, especially Far East, now universal, especially in summer months. *Epidermophyton interdigitale*, resembles *E. floccosum.* Often associated with mycotic infection of nails and palms of hands, resembling Hebra's *eczema marginatum.* Isolation of fungus difficult owing to contaminations. Now overcome by using potassium tellurite and penicillin to inhibit bacterial growth. Causes vesciles between toes and on inner margin or sole of feet, macerated skin of interdigital clefts, especially the fourth, persistent intolerable itching, often eczematous, secondarily infected. Deep cracks may develop. Common in swimming and Turkish baths. Dermatophytids or sensitivity eruptions may occur in subjects infected locally with fungi. This eruption usually subsides on treatment of the primary focus.

Diagnosis.—Scrapings soaked in *Liq. potassæ:* recognition of mycelium of fungus.

Treatment.—Often difficult. Whitfield's ointment (salicylic acid 1, benzoic acid 1, coconut oil 12, paraffinum molle 16 parts) applied for three weeks after feet have been soaked in hot water. Cignolin paint, tincture of merthiolate and merthiolate cream also much employed.

Prophylaxis.—*Carbon tetrachloride* applied to lesions said to be rapidly effective. Infected persons must take precautions against spread of fungus and should wear loofah slippers in bathroom.

As preventive measure application of lotion of liq. formaldehyde (40 per cent.) ʒ i, acid salicyl 3 i, alcohol and water equal parts ℥ viii recommended.

TINEA UNGUIUM.

Ringworm of nails. Common intractable fungous infection by *Trichophyton rubrum* or *T. mentagrophytes* of nails of hands and feet, especially in Europeans in India and China. Fungus gets under the free edge of the nail and grows back into the nail bed, and invades matrix, causing discolouration, ridging and fissuring of nail with black streaks.

Microscopic diagnosis.—Scrapings, made by piece of glass, boiled in *liq. potassæ*, and soaked for 24 hours ; fungus elements found especially in dark hæmorrhagic spots. Liable to confusion with eczema, syphilis, psoriasis and atrophied nails due to endocrine deficiences.

Treatment.—Scrape nail bed, soften lunule by potash and paint with tinct. iod. or 2 per cent. corrosive sublimate in alcohol, twice daily. Dressings kept in position by loose finger-stall. When advanced, only avulsion of nail is effective. Nail bed scraped and matrix dressed with acid salicyl. or hydrarg. ammon. ointment. Fuchsin paint (1 per cent.) (Castellani's paint) is well recommended. Extirpation of both nails and matrices may be necessary.

OTOMYCOSIS, " surfer's ear," " hot weather ear," or *otitis externa diffusa*, usually associated with coexisting fungous infection of other parts of body. Soreness and redness of external auditory meatus, pain on contact and on chewing. External auditory canal coated with moist sebaceous discharge. In severe cases inject penicillin. No evidence that fungi are main infective agents. Most common pathogen is *Ps. pyocyanea*.

Treatment.—Ear syringed and swabbed with spirit. Glycerine and ichthyol tampons inserted. Afterwards daily swabbings with spirit and fuchsin paint.

TRICHOSPOROSIS

PIEDRA.

Peculiar disease of hair of eyebrows, beard and scalp confined to native inhabitants in Brazil, Colombia and Guiana. Numerous gritty nodosities which look and feel like sand ; produces matting and knotting of hair. Spore-like bodies and small black nodules on hair shaft due to fungus—*Piedraia hortai* (*Asterineæ*), a family of fungi parasitic on trees. Nodule consists of tightly-packed stroma of brown hyphæ 4–8 μ in diameter known as *black piedra*; demonstrated by soaking in *liq. potassæ*, easily cultured on glucose agar, liquefy gelatin.

Diagnosis.—Easy, not to be confused with trichomycosis nodosa or trichorexis nodosa : non-parasitic malformation of the hairs.

Treatment.—Shaving affected parts.

TRICHOMYCOSIS NODOSA.—Fungous disease of hair common in Europe, C. Africa and Asia ; resembles piedra, but produces skin irritation and stains clothes, often red. Shafts of coarse hairs attacked, usually in axilla. Fungus: *Trichosporon beigeli;*

irregular nodosities; fungus elements 3–5 μ in length; cultured on Sabouraud's medium or beer-wort. Mycelial formation with arthro- and blastospores. Cultures and affected hairs have peculiar odour. May spread to skin and cause intertrigo. Mycelial elements seen in affected hairs.

Treatment.—Affected hairs washed in lotion of formalin 1 dr. (3·6 c.c.) to 6 oz. (177 c.c.) of refined spirit.

TRICHOMYCOSIS.—Trichonocardiasis, trichomycosis axillaris. Fungous disease of hairs producing skin irritation and staining clothes. *Nocardia tenuis*—causes hard mucilaginous substance in which pigment-forming cocci proliferate—black, red and yellow varieties.

Treatment.—Bathing with formalin and spirit ; applying mercurial ointment.

RHINOSPORIDIOSIS

A fungous infection of mucous membrance of nose, with polypi, tumours of cheek, conjunctivæ, lachrymal sac, uvula, rarely on penis. Occurs in Argentine, India, Ceylon, U.S.A., and is becoming increasingly common in Malaya and Indonesia. Due to *Rhinosporidium sceberi*, a yeast or phycomycete, spherical organism in polypoid growth (now thought by some to be a protozoan) ; oval spheres (6 μ) with chitinous envelope, vacuolated cytoplasm and vesicular nucleus. When fully grown, sporangium measures 0·25–3 mm., bursts and discharges spores which spread to connective tissue *via* lymph channels. Cultivated with difficulty on Sabouraud's medium.

Treatment.—Removal of polypi from nose by wire snare. Intravenous tartar emetic recommended.

CHAPTER VII

NUTRITIONAL DISEASES

(I.U. = International Unit)

BERIBERI

Endemic polyneuritis. Beriberi is a form of peripheral neuritis occurring in endemic or epidemic form in tropics and subtropics and also as a secondary manifestation in temperate climates.

GEOGRAPHICAL DISTRIBUTION AND EPIDEMIOLOGY

Formerly prevalent in Malaya, India, China, Japan, Philippines, throughout Central Africa, Panama, Australia (amongst Chinese). Has occurred in lunatic asylum in Dublin, in U.S.A., France, and Iceland, in Newfoundland fishermen and S. Atlantic whalers. All ages and sexes attacked, including breast-fed infants—" infantile beriberi " ; in ships—" ship beriberi " ; in asylums—" asylum beriberi."

ÆTIOLOGY

Associated with eating rice, especially white or polished rice. Funk (1911) isolated principle from rice-polishings (*i.e.*, rice bran) and originated term "vitamin." Since then many experiments have produced disease in man on vitamin-free diet; also in fowls, pigeons and rats.

Vitamin B_1, antineuritic, water-soluble vitamin. Isolated in pure state and synthesized as aneurin (thiamine, U.S.A.). Formula of hydrochloride: $C_{12}H_{18}ON_4SCl_2$. Normally in pericarp and germ of grain, especially rice. In greatest quantity in alcoholic yeast extract. Synthetic B_1 thermostable; can withstand 120° C. for 30 minutes. Necessary for growth and maintenance of mammals, birds, amphibians and insects, which can store and utilize it. Deprivation has immediate effect upon intake and metabolism. Main features of experimentally-produced B_1 deficiency in man: decreased sugar-tolerance, nervous symptoms, changes in temperature, visual deficiency, bradycardia, œdema. In endemic beriberi: B_1 content of diet 0·5 mg.; threshold 0·75 mg.

Modern view is not that B_1 is necessary for nutrition of nerves, but that it acts as a catalyst in carbohydrate metabolism, metabolizing pyruvic acid which otherwise accumulates in the cells, and can be detected.

Pyruvic acid in blood is not sign of toxæmia. It is found in blood, urine and C.S.F. in B_1 deficiency. (Normal 0·5 mgm. per 100 c.c.) 1,000–2,000 international units of B_1 (unit = 0·003 mg. or γ) or 3–6 mg. of crystalline B_1 restore pyruvic acid content to normal. Optimum B_1 estimated at 20 I.U. per kilo. Infants should receive 300 I.U. (or 1 mg.) daily; adults 700 I.U. B_1 is stored to a limited degree in liver, kidneys and heart, and is readily absorbed from small and large intestine. Excreted in urine and human milk in amounts varying with diet; less than 12 I.U. of B_1 in urine indicates deficiency.

In experimental animals deficiency is produced in 10 days to 9 weeks; in man, after few weeks' inadequate diet.

PATHOLOGY

Neuropathy in peripheral nerves, cord, spinal ganglia, nuclei of medulla, pons, cranial nerves, lymphatic system, vagi and phrenics. Membranes of brain and spinal cord congested. Degenerative lesions in antr. and postr. nerve roots. Degree dependent on duration of disease. Muscles supplied by these nerves show atrophy. Lesions in nerves not specific, but include neurological degenerations formerly ascribed to toxic agents, now believed due to B_1 deficiency.

Cardiac beriberi.—Size and weight of heart considerably increased, hydropic degeneration of heart muscle without evidence of true hypertrophy of muscle fibres.

Secondary pathology.—Pulmonary œdema, pressure atrophy of liver, spleen, kidneys, intestine, passive effusion fluid in serous cavities. Dependent œdema.

CLINICAL FEATURES

(1) Primary beriberi ; diet-produced disease.

(2) Secondary beriberi : now recognized in other forms of peripheral neuritis, *e.g.*, alcoholic, diphtheritic polyneuritis, Korsakoff's syndrome, Wernicke's encephalopathy.

Predisposing factors.—Lowering of body resistance by pregnancy, lactation, surgical operations, convalescence from dysentery, malaria or typhoid. Breast-fed babies suffer from beriberi from deficiency of vitamin B_1 in mother's milk.

Incubation period : weeks or months. Assumes various clinical forms according to extent and position of nerve lesion. Onset : insidious or sudden, usually apyrexial, though preliminary pyrexial polyneuritis sometimes noted. Mainly two forms :—

(1) Dry or paraplegic.
(2) Wet, cardiac, or œdematous.

1. **Dry.**—Paraplegia, usually of legs and arms, sometimes of intercostal muscles. Anæsthesia of front of tibia, sides of thighs; deep sensibility of tendo Achillis (Abadie's sign) lost. Muscular wasting, atrophy of gastrocnemii, hyperæsthesia of muscles—first gastrocnemii, then plantar muscles—fibrillary contractions, often myœdema or local zone of contraction on impact. Loss of fat. Reaction of degeneration (R.D.) present.

Deep reflexes (knee and ankle jerk) absent; superficial active. Ataxia on walking : foot-drop often. Beriberi of arms causes similar changes ; loss of muscular power, numbness of fingers, wrist-drop in extreme cases. Paralysis of intercostal muscles serious—death from respiratory complications. Paralysis of laryngeal muscles ; alteration of voice. In extreme cases herniation of abdomen, bulging of perineal muscles on expiration ; aphonia and explosive cough.

Sphincters and bladder normal ; appetite good ; digestion normal. Often combined with cardiac involvement.

2. **Wet or Cardiac.**—Enlargement of heart, pulsation of jugulars, loud systolic murmurs, reduplication of second sound, alteration in spacing—tic-tac rhythm—acceleration + on exertion, dilatation + on exertion, especially of R. auricle. Wide range in pulse pressure; low diastolic raised by adrenaline (Aalsmeer's test), used as indication of response to treatment. Diastolic pressure = minimum tone pressure; give adrenaline 1 mg., observe at 5-minute intervals). Auscultatory murmur persists during complete relaxation of pressure. Generalized anasarca ; face puffy ; lips cyanosed. Firmer œdema than that of nephritis, not involving scrotum. Low tension pulse ; may be bradycardia. Occasionally localized or fugitive œdema, associated with neuritis of legs. Loss of deep reflexes. Amount of urine reduced. In subacute or chronic forms gross right-sided cardiac hypertrophy, pulsation of pulmonary conus and aorta; *P.* wave accentuated.

Cardiac attacks (Shôshin : Japanese).—Sudden death from R. side cardiac failure + œdema of lungs. Also paralysis of diaphragm, acute dilatation of stomach, pleural effusion, hydropericardium.

Postmortem.—R. heart enlarged, conus arteriosus affected. Dilatation of veins. Intracellular œdema of heart muscle, sarcolysis. Hydropic degeneration primarily due to excess of lactic acid (defective oxygenation). Primary lesion : loss of contractibility due to water retention.

Course.—Uncertain ; may suddenly improve, then relapse, or assume malignant character ; usually clears up. In paralytic form : residual pareses or deformity, hyperæsthesia and muscular weakness.

Mortality.—Cardiac form in Malaya, high (formerly 80 per cent.) ; paralytic form, very low.

Atypical forms.—Rudimentary forms common ; partial patchy œdema, paralysis of diaphragm, ataxia of legs ; some of mixed type, with scurvy and pellagra, *e.g.*, ship beriberi and "Rand scurvy." "Chachaleh" of Somaliland is probably mixed beriberi and pellagra.

Secondary beriberi.—Polyneuritis with alcoholic poisoning, gastric carcinoma, chronic intestinal obstruction, ulcerative colitis (calling for operations on the gastro-intestine), cirrhosis of liver and evident alcoholic neuritis. Mixed cardiac types common in U.S.A. (curable by vitamin B_1), in polyneuritis of pregnancy with vomiting, and in diabetic neuritis. Defective assimilation with high metabolic rate responsible for B_1 deficiency. Dysfunction of cardio-vascular system from unbalanced diet common in U.S.A. and now in Britain. Tachycardia, bradycardia, gallop rhythm, vagal reflex irritability, dilatation of heart, arterial pulsation with "pistol sounds." Electrocardiograms normal in 7 per cent. of cases ; the main abnormal changes are in the T waves and prolongation of electrical systole Q-T.

B_1 deficiency plays primary rôle in precipitating disease ; metabolic rate similar to that of pure carbohydrate diet. Cardiovascular syndrome disappears before polyneuritis.

Infantile beriberi.—Distinct form in Egypt, Philippines, S. China Pacific Islands—scourge of Philippines. Differs in essentials from other forms. Never in Europeans, rarely in half-castes ; in breast-fed infants born of mothers affected with beriberi or on deficient diet causing absence of B_1 in milk. When children removed from breast, or artificially fed, cure results. Acute type resembles cardiac beriberi ; lasts ½–3 months ; child dies in convulsions. Acute heart failure, cyanosis ; head retraction and aphonia are marked features, ascribed to paralysis of left recurrent laryngeal nerve from pressure of left auricle.

Chronic form.—Progressive weakness and wasting, with periodic vomiting. No true paralysis, but loss of knee jerks. Pyrexia, vomiting and dysphagia presage death.

Infantile beriberi appeared in Pacific phosphate islands when restriction on toddy (fermented coco-nut sap) deprived natives of source of B_1. Balance restored by yeast preparations and cod-liver oil.

Wernicke's encephalopathy.—Ataxia, clouding of consciousness and ophthalmoplegia = superior hæmorrhagic polioencephalitis, originally associated with chronic alcoholism. Does not resemble infective encephalitis. Post-mortem hæmorrhages found in mamillary bodies of brain. First symptoms, persistent anorexia followed by vomiting and nystagmus, then paralysis of external rectus, loss of visual acuity, papillœdema, ptosis and retinal hæmorrhages. Rapid response to aneurin injections.

Nutritional retrobulbar neuritis.—Loss of visual acuity with disorders of perception. Usually pain and blind spot in retina. Paracentral scotoma, degenerative pigmentary changes round macula—occasionally optic atrophy. Associated in majority of cases with cardiac beriberi, though response to aneurin therapy disappointing.

Burning Feet.—Chronic condition associated with dietetic deficiencies, noted with beriberi as well as with pellagra, common in detention camps in last war in Far East. Deep aching in soles of feet spreading like toothache to instep and toes. "Pins and needles" worse at night, usually sleep impossible. Ascending skin analgesia, exaggeration, then loss of deep reflexes. Many develop retrobulbar neuritis and most have associated ariboflavinosis. Although nicotinic acid gives temporary relief, only real improvement is seen with large doses of aneurin.

DIAGNOSIS

In epidemic not difficult ; in sporadic cases by œdema of shins, palpitations, cardiac irregularity. **Jongck** (squatting) test—inability to rise from squatting position—hyperæsthesia of calf muscles, impairment or absence of knee jerk, and blood pressure tests :—

(1) Increase of diastolic sound after injection of adrenaline.
(2) Estimation of diuresis in fasting state with 1 litre of water.

Both restored to normal by injection of B_1.

Therapeutic test.—Administration of adequate B_1 for 10 days. Pyruvic acid determination : in acute beriberi, 2 mg. per cent. : in chronic beriberi, 1·5 mg. per cent.

Differential diagnosis.—From other forms of polyneuritis—alcoholic, diphtheritic, arsenical—triorthocresyl phosphate poisoning (ginger or "jake" paralysis) ; flaccid motor paresis ; tabes dorsalis ; pellagra, nutritional œdema ; nephritis ; myocardiac disease ; epidemic dropsy (*q.v.*) ; diabetic neuritis, Korsakoff's syndrome, Landry's paralysis. Chronic lead-poisoning shows the blue line, wasting of arms with exception of supinator longus ; also basophilic stippling of r.b.c. Beriberi distinguished from lathyrism by presence of knee jerk. Cardiac beriberi occasionally simulated by fluke infection (*Heterophyes, see* p. 190).

Prognosis.—Danger signs : dilatation of R. heart, pulsating jugular, dilatation of stomach, cyanosis, dyspnœa, paralysis of intercostal muscles, scanty urine, vomiting.

TREATMENT

Dry beriberi.—Diet. Elimination of white rice and substitution of peas, beans, oatmeal, yeast (*marmite*), proteins, eggs, milk, fat. Strict bed in severe paralytic and cardiac cases. Aneurin (B_1) specific, best injected subcutaneously. Soluble preparations of B_1 given by mouth are destroyed in stomach to great extent. *Betaxan* or *Benerva* for injection (25–30 mgm. daily) contains 2 mgm. aneurin per c.c. Total amount of aneurin arbitrary, depending on extent of paralysis (excretion of aneurin in urine now estimated with accuracy by thiochrome method : rapid excretion for 3 hours after subcutaneous or intramuscular injection).

For atrophy of muscles, faradism and massage after hyperæsthesia has abated. Hot air baths also. Prevention of deformity from muscle contraction and foot-drop by Phelps's talipes splint with elastic accumulator.

Cardiac beriberi.—Nurse as cardiac case. For orthopnœa : restriction of fluids ; saline aperient. For cardiac distress : 3–5 min. of 1 per cent. nitroglycerin—Oüabaine gr. 1/240 (0·27 mgm.) intravenously. Inhalations of amyl nitrite; bleeding, abstraction of 8–10 oz. (236–295 c.c.) of venous blood; oxygen inhalations.

Specific treatment.—Aneurin: maximum dosage, 3,000 I.U. (international units, p. 147). In acute cases, 1,000 I.U. intravenously into jugular vein; patient is restless after injection; effect is noted in one hour: rise of systolic and diastolic B.P. and corresponding increase of urinary flow. Repeat for return of symptoms.

Striking results of treatment.—Mortality rate formerly 80 per cent., now less than 8 per cent. Recovery usually in 14 days. Diet must be radically altered ; no white rice permitted or relapse will recur.

Infantile beriberi.—Infants removed from mother to wet nurse. Extract of rice polishings 5 c.c. daily as long as aphonia persists. Aneurin (if procurable) 1 mg. daily. Although symptoms alarming, recovery takes place in 3 days.

Prophylaxis.—Government control of rice. Too much milled rice not permitted. Educational methods advisable. Accessory foods encouraged. Diets containing large proportion of starch and sugar supplemented by foods containing B_1. Bread made from whole wheat flour contains B_1. When maize constitutes staple dietary, meal should contain germ. Prophylactic *marmite* in cubes (¼ oz., 7·7 gm.) twice weekly. Tinned meat is deficient in B_1 and addition of other foodstuffs necessary.

Body possesses no ample reserve of B_1 ; constant supply must be maintained.

SCURVY

Deficiency due to absence of vitamin C (ascorbic acid), characterized by swelling of gums, hæmorrhages into skin and mucous membranes. Identical with infantile scurvy. In tropics, occurs in epidemic form amongst labourers and workers on unsuitable dietary, especially natives accustomed to liberal fruit and vegetable diet.

ÆTIOLOGY

Typical food-deficiency. Ascorbic acid (now prepared synthetically): hexuronic acid, $C_6H_8O_6$; I.U. = 0·05 mgm. Destroyed by prolonged heat and drying; present in all vegetables and fruit, especially orange and lemon; absent from tinned fruits, preserved vegetables (peas and beans). Little in milk and meat. Cannot be synthesized by most mammals. Reappears during germination of yeast, and is synthesized by plants. Soluble in water and alcohol; more stable in acid than in alkaline media. Necessary for elaboration of collagen in tissues, for dentine, for osteoid matrix, chondromucin, and cell respiration.

Requirements for man = 400 units daily.
" " child = 800–1,000 units daily.

Normal persons have store of vitamin C. Normal output 33 mg. daily. In large doses causes increase of urinary secretion; in scorbutics excretion diminished.

CLINICAL FEATURES

Period of development: 4–8 months. Onset: insidious, loss of weight, emaciation, weakness, pallor, stiffness in leg muscles; swelling of gums; fungating masses project beyond teeth, which loosen and fall out. Swollen tongue; enlarged salivary and lymphatic glands. Skin dry and rough. Albuminuria and constipation usual, sometimes diarrhœa.

Hæmorrhages.—Subcuticular bruising; purpuric rash; petechiæ round hair follicles, especially on thigh; intra-articular effusions into knee; subperiosteal nodules; œdema of ankles. Hæmoptysis or hæmatemesis. Cardiac distress, irregular pulse, hæmic systolic murmurs. Headache early, delirium later. Necrosis of jaw in advanced disease.

Complications.—Gangrene of lungs from septic inhalation. Night blindness frequently ascribed to vitamin C deficiency in tropics. May co-exist with beriberi, sprue, pellagra and other diseases.

In children "scurvy rosary" at junction of costal cartilages; separation of epiphyses of long bones.

Varieties.—"Rand scurvy," no spongy gums or neuritic signs of beriberi; primary hypertrophy, secondary dilatation of heart. Reflexes exaggerated. Predisposition to bacterial infections, especially pneumonia.

DIAGNOSIS

On clinical grounds easy. Constriction of arm by band of sphygmomanometer compresses arm to 90 mm.: on fading of cyanosis petechial spots become visible, indicating capillary permeability.

Intradermal test.—Dichlorophenol-indophenol 1/100 c.c. injected; time for decolourization of tissues is measure for vitamin content: 5 mins. = tissue saturation; 10 mins. or longer = vitamin C deficiency.

Estimation of vitamin C saturation in normal person : large dose causes rapid excretion in urine ; in scurvy retained in body. Give 600 mgm. ascorbic acid ; urine in 3–6 hours should contain 5 mgm. per cent. (titrate against dichlorophenol-indophenol).

Differential diagnosis.—From acute myeloid, lymphoid leukæmia or hæmorrhagic diathesis.

TREATMENT

Chiefly dietetic. Fruit, vegetables, lemon juice, fresh meat, germinating peas. Ascorbic acid by mouth or intravenously 40–100 mg. (0·6–1·54 gr.) daily. Hydrogen peroxide mouth-wash for gums.

INFANTILE BILIARY CIRRHOSIS

Geographical distribution.—Frequent in India. General features resemble Lænnec's cirrhosis ; nutritional basis indisputable. Also in Dutch E. Indies ; sparingly in Mexico and China.

Ætiology.—Prevalent in Hindus (not Moslems or Europeans), especially vegetarians and overfed and pampered children aged 6–24 months ; usually commences during dentition ; fatal in from 3–8 months ; rarely may commence within few days of birth and be fatal in 3 weeks. Both sexes equally susceptible. Family disease. In Bengal, Bombay, and United Provinces ; commoner in rural districts than in towns. Possible connection with cows' milk ; breast-fed children escape. Association with bacillary dysentery suggested. Urine may contain *Bact. coli* and *B. alkaligenes*. *B. coli* also isolated from liver. Now suggested that fatty liver disease in childhood (malignant malnutrition) may later lead to biliary cirrhosis.

Pathology.—Intercellular, lobular, biliary cirrhosis (Lænnec). Formation of new bile-ducts ; subacute toxic cirrhosis ; regeneration ; adenomata of hepatic cells. Liver small, hard and bile-stained. Compensatory splenomegaly usual. Ascites +.

Clinical features.—Onset insidious. Ascites, œdema of hands, feet and eyelids. Cholæmia, icterus, pyrexia usually, thirst, clay-coloured stools, urine : bile + and occasionally *B. coli*. Deep bronzing as in Addison's disease. Terminal gastro-intestinal hæmorrhage. Death from cholæmia.

Blood.—Microcytic anæmia ; leucocytes 8–14,000–50,000 in terminal stages, mainly lymphocytes. Arneth count : shift to left. W.R. negative.

Treatment.—Substitution of modern infant foods for cows' milk has prevented further cases in cirrhotic families. Recovery follows change of food in 6–10 weeks.

Prophylaxis.—Proper feeding of expectant mothers : 2–3 oz. fresh fruit daily. (Vegetables deficient in India.) Iodized salt added to food.

PELLAGRA (ALPINE SCURVY)

Endemic disease of slow evolution, diet deficiency. Complex syndrome : nervous, alimentary and cutaneous, with seasonal incidence. Confined to rural population. As in beriberi has two stages : (1) primary, (2) secondary.

GEOGRAPHICAL DISTRIBUTION AND EPIDEMIOLOGY

Almost universal. *Europe:* Spain, Portugal, S. France, Italy, Austria, Hungary, Balkan States, Poland, Russia. Also a few from Germany and Britain. *Africa:* W. Africa, Egypt, Sudan, Red Sea, Rhodesia, Nyasaland, Zululand, Union of S. Africa, Tanganyika, Kenya, Gold Coast. *Asia* : Asia Minor, India (sparingly), Malaya, Philippines, Japan, China, Korea, Manchuria. *America* : Canada, South U.S.A., Mexico, Central and S. America, W. Indies (esp. Jamaica, Barbados). *Australasia* : a few cases in S. Australia and New Caledonia.

Fluctuation from year to year. Long periods of quiescence. Not infectious or contagious. In epidemic form in spring and autumn months. Egypt : April–May, October–November. Nyasaland : August–October, January–March. Barbados : May–October.

Sex and occupation.—Both sexes liable in U.S.A. ; more in women (17–40, from debilitating effects of menstruation, parturition, etc.). Common in children in South U.S.A. Field labourers especially liable ; inhabitants of towns escape, even in heart of endemic areas.

Pellagra in Britain.—Attention was drawn to pellagra in England in 1912 ; then it was discovered in London hospitals, later in lunatic asylums and other institutions, especially Lancashire Mental Hospital. From 1922 onwards, numerous deaths from pellagra recorded in asylum inmates. Secondary pellagra now commonly noted, associated with chronic intestinal disease.

Infantile pellagra.—Especially in Central, W. and E. Africa ; sometimes considered a separate disease.

Predisposing causes.—In time of stress and war, great increase in pellagra, as in Turkish armies in 1918, noted also in national disasters, as after great Misissippi floods in 1927. Pellagra disappears under improved hygienic and dietetic conditions, *e.g.*, in Italy.

ÆTIOLOGY

Formerly ascribed to consumption of maize, first in Italy, later in South U.S.A. Certain proof that disease is still most common in countries where maize is staple article. Influence of sunlight on skin manifestations noted by Italian observers, who reproduced rash on limited areas of skin exposed to sun. In 1912 Funk first suggested analogy between pellagra and scurvy as food deficiency. Later, disease reproduced in America on protein-deficient diet. Biological protein value theory tested out in Turkish prisoners of war in Egypt in 1919.

Black tongue disease of dogs (canine typhus) found by Goldberger to be analogous to human pellagra, curable by yeast and liver (1922). P.P. (pellagra-preventive) factor stipulated proved identical with vitamin B_2—nicotinic acid and nicotamide.

Nicotinic acid.—Carboxylic acid of pyridine (by oxidation of nicotine) ; essential substance in meat infusions necessary for growth of bacteria. Nicotinic acid and nicotamide cure black tongue in dogs, nutritional disease of pigs and pellagra in man. Functions in body unknown, but nicotamide part of molecule and co-zymase are essential for carbohydrate metabolism. Liver, kidneys, milk, eggs and cheese are richest sources of nicotinic acid.

Riboflavin (lactoflavin).—Also concerned in pellagra syndrome, a yellow fluorescent pigment in liver, eggs and milk, imparts greenish colour of whey. Isolated in pure state and synthesized. Chief supply derived from meat and milk. Characteristic sign of riboflavin deficiency in animals : failure of growth. Concerned with oxidation in body tissues, not synthesized by the organism, essential for cellular respiration. Deficiency in man (ariboflavinosis) exposed by angular stomatitis with fissuring (cheilosis), seborrhœa, acne rosacea, possibly interstitial keratitis—signs associated with pellagra.

Summary.—Pellagra due to ill-balanced diet ; can be prevented by suitable dietary alterations and by addition of vitamin B_2 complex.

PATHOLOGY

Main features often obscured by co-existing disease, especially bacillary dysentery and tuberculosis. General atrophy, emaciation, deep pigmentation of viscera, brown atrophy of heart, atrophic changes in suprarenals, some atrophy of brain, distension of lateral ventricles, degeneration of lateral columns and crossed pyramidal tracts of cord, atrophy of anterior cornual cells.

Microscopic changes.—Chromatolysis and disappearance of Nissl's granules in posterior spinal ganglia ; marked chromatolysis of Clarke's columns, Betz cells of cortex and Purkinje cells. Resemblance to central neuritis and subacute combined degeneration of cord. No changes in C.S.F.

CLINICAL FEATURES

Prolonged course. Note regular periods of quiescence and exacerbation. May last for years. Diagnostic triad—*dermatitis, diarrhœa, dementia.*

Prepellagrous symptoms (larval pellagra).—Frequent and may escape detection : stomatitis, raw red tongue, as in sprue, with angular stomatitis, atrophic, scaly lips (*perleche*) ; bleeding, swollen gums ; conjunctivitis with lacrymation ; seborrhœic excrescences on naso-labial folds, alæ nasi, and bridge of nose. Roughened skin over knees and elbows ; *phrynoderma* or " toad skin." Often no further symptoms noted.

Digestive symptoms.—Nausea, vomiting, flatulence, diarrhœa, often steatorrhœa, resembling sprue; meteorism +. Epigastric and abdominal tenderness.

General appearances.—Tense, staring look; irritable, stupid, morose; headache, pains in loins and back.

Skin symptoms.—Dermatitis may be earliest symptom noted, but is usually secondary to general metabolic disturbance; symmetrical, characteristic erythema, like sunburn, on exposed parts: back of hands, dorsum of feet, forearms, chest, neck, face (butterfly patch), and usually on scrotum or female genitalia; symmetrical patches behind mastoid processes, spreading downwards round neck like collar (Casal's necklace). Areas affected are tense, swollen, burn and itch on exposure to sun; petechiæ, bullæ, and fissures common. After 14 days: desquamation, hyperkeratinization, roughened sepia-pigmented skin which gives the condition its name: *pelle* (skin), *agra* (rough). Atrophy of intrinsic muscles of hands is common, causing a wrinkled appearance (washerwomen's fingers); colour of skin naturally varies in different races—blackish-purple in negroes. Burning sensation of feet and hands possibly due to liberation of histamine. Local œdema of legs and generalized anasarca not uncommon in acute cases. With each recurrence of dermatitis pigmentation is increased.

Nervous symptoms.—Tremors, especially of tongue. Deep reflexes +: ankle clonus. Mid-dorsal spinal tenderness. Muscular cramps, insomnia, stupor, vertigo, tendency to fall backwards or forwards. Hands and feet burning. Chvostek's sign occasionally. Pyrosis—burning in œsophagus—and depression, melancholia, maniacal interludes, suicidal tendencies. Gait uncertain, spastic paraplegia, epileptiform convulsions. Finally: complete dementia, paralysis, incontinence of urine and fæces, bedsores, death. Whole course variable; usually 10–15 years.

Variation in type: obscure forms.—*Pellagra sine pellagra*, commoner than fully-developed disease. **Larval pellagra:** glossitis, angular stomatitis, atrophic changes in lips (perleche). In some, nervous symptoms predominate: in others gastro-intestinal or cutaneous. Ocular involvement occasional: ptosis, diplopia, amblyopia, mydriasis. *Acute rapidly fatal form:* "pellagra typhus," pyrexia, prostration, muttering delirium, tremors +, rigidity, convulsions. Death in 3 months.

Pellagra in children.—May be overlooked in native races: irritable, skin and hair lose normal colour and gloss, diarrhœa, transient œdemas; then pigmented patches on extensor surfaces of wrists, ankles, knees and elbows.

Clinical pathology.—Blood: secondary anæmia usual, but may progress. Occasionally true pernicious picture. Leucocyte count normal, but constant lymphocyte increase. Indirect positive Van den Bergh test +, no change in corpuscular fragility. Plasma albumin diminished. Gastric juice: constant hypochlorhydria, often achlorhydria. Urine: alkaline, casts, indican, coproporphyrinuria (formerly considered distinctive of pellagra) specially noted in alcoholic secondary pellagra.

SECONDARY PELLAGRA.—Pellagra may lead to insanity, but mental patients in asylums are liable to pellagra after 6 months.

Pellagra may be due to voluntary restrictions—slimming, or even ketogenic diets.

Pellagra in all its manifestations may be associated with organic lesions of gastro-intestine : œsophageal stricture, carcinoma of stomach, pyloric ulcer or stenosis, carcinoma of ileum, rectal stricture, polyposis, chronic amœbic or bacillary dysentery, cœliac disease, idiopathic steatorrhœa, sprue.

Alcoholic pellagra.—Seen in chronic alcoholics in U.S.A., especially with methyl alcohol. Glossitis and angular stomatitis marked in these cases ; often associated with alcoholic neuritis.

Prognosis.—4–10 per cent. become permanently insane. Melancholia usual, but general paralytic type sometimes.

DIAGNOSIS

Difficult in larval and atypical cases. Made on clinical grounds assisted by clinical pathology.

Differential diagnosis.—Rash to be distinguished from acrodynia, erythema multiforme, dermatitis venenata, eczema, trade dermatitis, lupus erythematosus, malignant malnutrition (kwashiorkor), Plummer-Vinson syndrome. Gastro-intestinal symptoms resemble sprue. Nervous manifestations from hysteria, general paralysis, ergotism and lathyrism. " Pink disease " in children may be mistaken for pellagra. Crazy-pattern skin lesions—extremely common on legs of undernourished natives—are not pellagrous.

TREATMENT

High protein diet : liver, yeast extracts (" marmite "). Nicotinic acid by mouth, 200–1,500 mgm. (3–22·5 gr.), daily over considerable period. Larger doses necessary for nerve involvement ; also injection of 40–80 mgm. ; apt to produce nicotinic reaction—arterial pulsation, flushing, sometimes œdema. Routine dosage : 300 mgm. (4·5 gr.) of nicotinic acid daily. Similar results with nicotamide. Glossitis and aphthous stomatitis healed in five days. For angular stomatitis : riboflavin, 3 mgm. (0·45 gr.), daily. Overdosage with nicotinic acid : tingling and numbness of tongue and pain in lower jaw. Treatment controlled by estimation of coproporphyrins. Other forms of mental disease—*e.g.*, paranoia—now being treated with nicotinic acid or coramine (diethylamide of nicotinic acid). Pyrazine monocarboxylic acid and quinolinic acid have action similar to nicotinic acid.

Prophylaxis.—Mainly improvement in dietetic standards. Maize flour as standard diet prohibited.

KWASHIORKOR (Malignant Malnutrition)

Kwashiorkor is a common tropical childhood disease taking its name from a West African term " red man or boy " and denoting pigmentary changes in the hair. It is nutritional in origin leading to damage of liver and pancreas and all intestinal organs, thereby producing œdema, hypo-albuminæmia, hair changes, depigmentation of skin, fatty diarrhœa, reduced resistance to cold and stunted growth.

Ætiology.—Multiple deficiencies are involved, but other avitaminoses are commonly associated. Seasonal alterations in food supply alter the pattern of incidence. In West Indies the greatest incidence is from January to April. It is quite distinct from "infantile pellagra." Found mostly in neglected ill-fed, illegitimate children of 6 months to 4 years. Mortality 60 per cent. in late breast-feeding, weaning and post-weaning age. Cereal and carbohydrate diets combined with lack of milk mostly involved.

Pathology.—Enlarged fatty liver, necrotic foci in pancreas and atrophy of acini. Fatty infiltration from the periphery to centre. Fine fibrosis may lead later to cirrhosis. Those organs most concerned with protein metabolism themselves most vulnerable to protein deficiencies.

Clinical features.—Sick, œdematous, undernourished child with depigmented scaly skin. Rhagades and cracks at mucocutaneous junctions. Emaciation with diarrhœa. Hair changes (*achromotrichia*) constant. Hair scanty, straight, silky, bleached to reddish tinge. Eyebrows often absent. Skin changes, loss of pigment and dermatoses. Pale reddish colour, easily noticeable on face with circumoral depigmentation. Rash on extremities; desquamation leaving depigmented oozing surface and forming crazy-pavement skin. Deep necrotic ulcers may form and also gangrene of limbs. Oedema mainly confined to legs, may be generalized and fatal.

Diarrhœa constant. Stools fatty, semifluid, offensive, resemble those of cœliac disease.

Mental changes.—Dull, apathetic miserable uttering low whimperings. Lack of resistance to cold. Extremities frigid, even in hot weather; anorexia constant.

Stunted growth.—Makes estimation of age difficult. Weight normal for first 9 months. Maximum retardation from 2 to 4.

Diagnosis.—Serum proteins reduced. Increased globulins. Liver function tests, value below 10 per cent. Blood shows reduction of hæmoglobin to 9 gm. per cent. with 3½ million erythrocytes. Megaloblastic bone-marrow. Liver biopsy fatty infiltration in grades I and II. Steatorrhœa—mean total fat 30–40 per cent. Differential diagnosis from hunger œdema, infantile pellagra and cœliac disease.

Treatment.—Diet all-important. Milk essential when disease is advancing—changes are irreversible. Maize meal avoided. Minced meat with vegetables and soup. Anorexia makes feeding difficult. Powdered hog's stomach advised. Blood transfusion into jugular vein every day for one week or longer. Return to normal dietary postponed till all symptoms have disappeared. Oedema occurs with muscular wasting, so all patients responding to treatment lose weight at first.

TROPICAL SPRUE (Psilosis, Ceylon Sore Mouth)

(P.A. = Pernicious anæmia. HCl. = Hydrochloric acid.)

Syndrome : glossitis, emaciation, megalocytic anæmia, steatorrhœa, of long duration in tropical countries. Resembles idiopathic steatorrhœa, sometimes known as "non-tropical sprue", also cœliac disease in children.

GEOGRAPHICAL DISTRIBUTION AND EPIDEMIOLOGY

Particularly in India and S. China, Ceylon, Philippines, Mauritius, N. Australia ; rarely in Pacific Islands. Central Asia (Transcaspia). W. Indies (Porto Rico), South U.S.A., Central and S. America. Rarely in N. Africa, Palestine, Syria, and S. Italy. Apparently absent from Central Africa. Sometimes has seasonal incidence. In India and Ceylon at 6,000 ft.

Europeans especially liable, but may occur in Indians, especially those who have adopted European life ; rare in indigenous natives; almost unknown in negroes ; Chinese and Japanese liable.

Both sexes equally liable in third and fourth decade ; unknown in small children (youngest reported 11) ; not common in young adults. Husband and wife may be attacked at same time.

Popular theory in Ceylon and India of association with housing—sprue bungalows (" dry rot " in walls), but no universal connection.

ÆTIOLOGY

Initial cause still obscure. Remarkable characteristics.

(1) **Latency:** may commence 25 years, or even longer, after quitting endemic area.

(2) **Remissions:** disease may recur 20 years or more after initial attack.

(3) **Long residence** in endemic area formerly considered necessary (2–3 years or more). In recent war in Burma from 1942–1945 sprue behaved like epidemic disease with a short incubation period ; in some instances two weeks. Sprue appeared on an unprecedented scale in widely separated areas—unconnected with dietetic or climatic factors. There it observed distinct regional distribution, though confined to India and Burma. It was absent amongst troops in the Pacific combat zone. Three quarters of the cases had less than two years' service. In 1944 some 675 British soldiers were invalided to England with sprue. Seasonal incidence in E. India lasted from March to September, but peak incidence in June which corresponded with the fly season and outbreaks of bacillary dysentery.

Possibly to fit in with all peculiarities sprue may be virus infection. Dietetic cause suggested, but difficult to prove. Sprue syndrome is expression of chronic jejuno-ileal insufficiency (Bennett). Main signs and symptoms common to other diseases in which there is damage to absorptive surface of small intestine. Interference with normal absorption of proteins, sugar and especially of fats. Mechanism of fat absorption probably same as in cœliac disease and idiopathic steatorrhœa.

N.B.—Several factors are common to sprue, pellagra and P.A. they may merge into one another ; therefore border-line cases occur.

PATHOLOGY

Skin dry, rough, lemon-yellow. Emaciation +; absence of subcutaneous and omental fat. Atrophy of liver +, sometimes fatty degeneration. Heart: brown atrophy. Diaphanous distended small intestine; many changes formerly described due to post-mortem changes. Discrepancy in different accounts. Generally considered that villi are shrunken, atrophied, with subacute inflammatory changes, and sometimes ulceration. Mesenteric glands enlarged and fibrotic. Bone marrow hyperplasia, as in pernicious anæmia. Death usually from intestinal atrophy, anæmia, perforation of ileum.

Clinical pathology.

Fæces: steatorrhœa, large, copious, acid, sour odour, contain bile; 5 times normal size; excess of fat 50 per cent. or more; colour masked by fat and alteration of bile pigments; excess of fatty acids three times that of neutral fat; fatty acid crystals and fat droplets seen in microscopic preparations. Indications that pancreatic function is normal: fat is split, but not absorbed. Low fat content of blood (412·8 mg. per cent.—normal 600 mg. per cent.). Sigmoidoscopy shows rosy red injection of intestinal mucosa.

Urine: in acute stage, urobilin +, coproporphyrinuria, indican.

Gastric juice: usually hypochlorhydria; in cases with severe anæmia, achylia gastrica (unlike pernicious anæmia, HCl. returns under successful treatment). Gastroscopy shows atrophy of gastric mucosa as in P.A.

Blood: anæmia pronounced, usually megalocytic with anisocytosis and polychromasia; normoblasts rare. Colour index above 1 (as in P.A.). Most severe anæmia in elderly patients. Hæmolytic crises not uncommon. Hyperbilirubinæmia usual, though not as high as in P.A. Price-Jones curve as in P.A. Hypocalcæmia in well-marked cases (8–9 per cent., normal 11). Hypocholesterolæmia. Flat blood-sugar curve (as in idiopathic steatorrhœa).

Explanation of steatorrhœa (mechanism of fat absorption).—Possibly result of functional pathology of absorptive surface of villi. Primary cause may be abnormal gastric function.

CLINICAL FEATURES

Great variability. Usually chronic and intermittent; may last 10–15 years or longer. Three cardinal symptoms: glossitis, meteorism, diarrhœa. Diarrhœa in early morning, sometimes nocturnal. Meteorism excessive after food, especially at night.

Secondary sprue.—Not infrequent sequel to other intestinal diseases, such as bacillary or amœbic dysentery, often after malaria. In women during pregnancy or parturition.

Mouth symptoms.—Usually precede diarrhœa—not always. Not invariably present. Sometimes noticed for a year before diarrhœa. Glossitis v. painful, accompanied by taste loss and often by salivation; in extreme cases by angular stomatitis (as in pellagra); varies from day to day. Extremely sensitive, especially to salts and acids. Frequently evanescent aphthæ on tip or under-surface of tongue, lower lip and buccal mucosa. Glossitis aggravated during exacerbations. Inflammation of fungiform papillæ, atrophy of filiform. *Larval or presprue glossitis* may precede fully developed syndrome.

Dyspepsia.—Epigastric oppression, gaseous distension after meals, borborygmi.

Dysphagia.—Œsophageal pain not uncommon, especially in anæmic patients.

Tetany and cramps.—In longstanding cases (hypocalcæmia) : Trousseau's and Chvostek's sign occasionally.

Diarrhœa.—Acute in early stages, usually early morning diarrhœa, may be watery, frothy, copious, containing undigested particles, but always offensive and accompanied by flatulence +. Excoriation of anus not uncommon ; in women pruritus vaginæ also.

Temperament.—" Spruey "—unreasonable and irritable. Longstanding cases may be partially demented. Memory defective ; loss of powers of concentration. Dusky pigmentation of skin not infrequent. In women usually amenorrhœa.

Types :—*Gastric.*—Glossitis, gastric oppression and distension; no diarrhœa, but large fatty stools.

Intestinal.—Diarrhœa and fatty stools, emaciation and anæmia ; glossitis absent or may appear as terminal phenomenon.

Mild.—Steatorrhœa without diarrhœa, slight anæmia ; no emaciation.

Sequelæ.—Severe anæmia resembling P.A. frequent sequel after apparent recovery ; may sometimes be difficult, except by achylia gastrica, to differentiate from P.A.

Subacute combined degeneration of cord : very rare.

Other avitaminoses : scorbutic symptoms occasionally; tingling and paræsthesia with loss of reflexes (avitaminosis B_1); ariboflavinosis.

Œdema of extremities : not uncommon, probably nutritional.

Dermatitis not uncommon, sometimes definitely pellagrous.

Secondary sprue.—Sprue symptoms secondary to bacillary or amœbic dysentery, or often intestinal disease, especially hill diarrhœa (*q.v.*).

Mortality.—Now small (1·5 per cent.). Death from asthenia, severe anæmia, sometimes perforation of ileum, rarely thrombosis of mesenteric veins.

DIAGNOSIS

On clinical appearances, especially on analysis of fæces and megalocytic anæmia. Note *absence of osteoporosis.*

Differential diagnosis.—From *cœliac disease* ; resembles sprue, but always in infants. Glossitis not usually present.

Idiopathic steatorrhœa. Probably cœliac disease in adult life : skeletal changes, *osteoporosis*, infantilism, megacolon, clubbed fingers, brittle nails, lens opacities ; fine, silky hair ; glossitis usually (but not so marked as in sprue) ; anæmia variable, usually not severe, usually hypochromic. Does not react so favourably to treatment with folic acid and liver extracts.

Pancreatitis.—Alkaline fatty stool, free fat is in excess of neutral fat and soaps.

From P.A.—Not always easy ; achylia gastrica without response to histamine. No steatorrhœa.

Sometimes from *Addison's Disease* (low B.P.).

Gastrojejuno-colic fistula, malignant disease of mesenteric glands and tabes mesenterica may simulate sprue.

TREATMENT

Removal from endemic area essential. Sprue cases do not do well in heat. Improvement on voyage to England usual. Bodily and mental rest essential. Strict bed till diarrhœa ceases. In cold climate, patient must be kept warm. Nursing important. Stools weighed daily. Diet very important : high-protein diet with liver and minced meat. Milk no longer considered a cure, but where assimilation is grossly impaired and glossitis is acute, specially prepared "Sprulac"* is beneficial. Small quantities at frequent intervals. Convalescent diet important : fats and starches carefully controlled. Fruit advantageous, especially bananas and strawberries.

Specific treatment.—Folic acid (folvite) should be commenced directly diagnosis is made. Effects first seen on glossitis and mouth symptoms. Appetite improves and diarrhœa abates. Weight increases. Dose for adult 30 mgm. daily for 10 days, 20 mgm. for an equal period and thereafter 5 mgm. daily as maintenance dose. In order to prevent neurological manifestations folic acid must be combined with liver therapy. Thymine (5 methyluracil) in doses of 6 gm. daily for 14 days may be substituted, also teropterin.

Medicinal treatment.—For diarrhœa: collosal kaolin, sulphonamides —sulphasuccidine.

For meteorism : injection of pitressin, ½–1 c.c. Small doses of ol. ricini.

For glossitis : glauramine (acriflavine mouth wash). For angular stomatitis : riboflavin, 3 mgm. daily.

For anœmia : liver injections in large amounts ; 4 c.c. alternate days for severe cases for 12 injections ; most efficient preparations : *campolon, anahæmin, hepatex, examen.* Vitamin B_{12} (*cytamen*), 15 μmg. injected intramuscularly twice weekly (1 c.c.) is followed by rapid hæmatological response. In extreme cases blood transfusion most beneficial. Reservoir dosage of liver extract : 2 c.c. weekly during convalescence.

For dyspepsia : acid hydrochlor. dil., 20–30 min. (1·2–1·8 c.c.) t.d.s.

Progress.—Folic acid 5 mgm. daily for 6 months plus liver injections. Effects of modern treatment very good. Cessation of diarrhœa, improvement in colour and size of stools, increase of weight. Improvement of blood. Severe cases recover in 1–2 months.

Prognosis.—Good under present conditions and after prompt removal from tropics. Return to tropics inadvisable before a year at least free from symptoms. Relapses likely, especially if over 50 years, in extremes of climate, hot or cold.

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* From "Cow and Gate Ltd.", also chemists.

HILL DIARRHŒA

Resembles incipient sprue and regarded as initial stage of it. In Europeans at high altitudes (above 6,000 ft.) in Himalayas, also said to occur in S. Africa and S. America, but doubtful. Liquid, offensive steatorrhœa as in sprue; meteorism and flatulence. No glossitis or stomatitis. Abates usually on removal from endemic area, but may merge into sprue. Has been ascribed to abdominal chill, mica in water and other causes. True ætiology still obscure.

Treatment.—Hydrochloric acid and pepsin mixtures. Probably also reacts to folic acid.

CHAPTER VIII

CLIMATIC DISEASES

HEAT STROKE, THE EFFECTS OF HEAT

Moist heat most important; air temperature, wind velocity and relative humidity also contribute. In calm air human body can support air temperature of 100° F., if relative humidity is less than 90 per cent.; 120° F, if humidity less than 40 per cent., 140° F. if humidity less than 15 per cent. Death occurs at 128° F. with wind velocity of 20 miles per hour ; at 117° F. with wind velocity of 56 miles per hour.

I. HEAT EXHAUSTION

Faintness is brought on by exposure to high atmospheric temperature. Collapse is attributable to physical exertion in hot environment in absence of salt deficiency. Symptoms and signs similar to those after exertion in ordinary environment, but relatively more severe. Exertion is stopped at stage of exhaustion, but collapse may occur taking the form of syncope.

Salt deficiency heat exhaustion and collapse.—Attributable to inadequate replacement of salt loss in hot environment leading to dehydration and oligæmia. Symptoms and signs are similar to hypochloræmia under ordinary conditions. For prevention increase salt intake to 28 gm. (1 oz.) daily. Fluid up to 16 pints. May be chronic with asthenia, or acute with collapse, pallor, sweating, vomiting and sometimes muscle cramps. Urine scanty, concentrated, free from chlorides. Hæmoglobin concentration and plasma protein raised. Relieved by restoration of blood chlorides.

Water deficiency heat exhaustion and collapse.—Attributable purely to lack of drinking water in hot environments. Thirst discomfort, anorexia, weariness, eventually dyspnœa and cynosis. Finally inability to stand erect, restlessness and dilirium. Relieved by water replacement.

Anhidrotic heat-exhaustion and collapse.—Attributable to chronic sweating deficiency. Associated with, or preceded by, severe prickly heat and skin changes—*Miliaria profunda.* Symptoms may be present when at rest if area of sweating deficiency is large or heat very great. Aggravated by exertion. General mental and physical asthenia, difficulty in concentration and in sleeping. Eventually collapse with loss of consciousness. After exposure to heat stress skin is dry except on face, palms, soles and axillæ. Slow to return to normal sweating.

Heat cramps (Miners' cramp; Stokers' cramp).—Attributable to salt deficiency in hot environment. Painful spasms of voluntary muscles, usually following activity and precipitated by drinking unsalted water. Relieved by administration of salt.

Sunburn.—Attributable to exposure to sunlight. Acute erythema, if extensive may cause malaise, headache, fever and occasionally vomiting. May interfere with heat-regulation, when affected areas lose vasomotor control and do not sweat.

Prickly heat (Miliaria rubra).—Attributable to extensive sweating accompanied by prickling (see p. 168). Generalized anhidrosis may follow prickly heat.

Acute heat neurasthenia.—Attributable to short-term exposure to hot environment, in absence of salt water or sweating deficiencies. Symptoms of fatigue, tiredness, disinclination to work, irritability. Partly attributable to inadequate adaptation of circulatory system.

Chronic heat neurasthenia.—May simulate " effort syndrome." Loss of energy, initiative and interest. Loss of weight and appetite, fall in standard of performance. Symptoms relieved after removal from environment.

Heat œdema.—Attributable to alteration in vasomotor system during acclimatization to heat. Œdema of extremities, especially ankles. May produce incapacitating swelling. Usually transient.

II. HEAT-HYPERPYREXIA

(Heat stroke. " Siriasis ")

It is an acute condition in high atmospheric temperature, with hyperpyrexia, coma and pulmonary œdema. Heat-hyperpyrexia is an exaggeration of heat exhaustion.

Geographical distribution and epidemiology.—Restricted endemic areas. In America, in summer in big towns on East Coast, Mississippi Valley, Gulf of Mexico, Amazon and La Plata. Valleys in S. America. In Africa, the Nile Valley, coasts of Red Sea, Algeria, Syria, Iraq. In India, valleys of Indus and Ganges, Lower Burma, Tonquin, S.E. China. In Australia, Murray River, Queensland Coast. Usually when atmospheric temperature is from 120–130° F. in shade.

Ætiology.—Europeans, especially newcomers, more liable than natives or longstanding residents. All ages and both sexes are liable; men more than women, on account of their habits. Attributable to failure of heat-regulating mechanism peripheral or central; may occur following known generalized anhidrosis. Atmospheric heat on body, overheating of blood, auto-intoxication; indican, acetone and diacetic acid in urine. Suppression of sweat precedes onset of serious symptoms, exhaustion of sweat apparatus. Skin hot and dry.

Hypodermic injections of atropine predispose to heat stroke.

Pathology.—Rigor mortis early. Blood: fluid, congestion of venous system and right side of heart; blood and muscles acid in reaction. Heart in rigor mortis, contraction of left ventricle. Venous congestion of meninges, necrotic changes in ganglion cells of brain with chromatolysis of nuclei. Cerebrospinal fluid and pressure increased. Intestinal mucosa swollen and congested. Temperature of cadaver rises after death to 114° F.

Clinical features.—Heat-hyperpyrexia develops independently of exposure to sun, often during night: pains in limbs, vertigo, headache, mental confusion, anorexia, thirst, photophobia, chromatic aberrations of vision, suffused eyes, vomiting, suppression of sweat, urinary irritability, loss of knee-jerks. Then: restlessness, wild delirium, coma, hyperpyrexia (to 110° F., 43·3° C.). Pupils contracted, deep reflexes absent, diarrhœa +, skin emanates mousy odour, urine often shows red blood corpuscles, albumin and casts.

Dehydration of blood with concentration of hæmoglobin to 110, polycythæmia and leucocytosis, diminution of blood chlorides and plasma bicarbonate; rise in lactic acid, blood sugar and urea. Hypochloræmia seen by low urinary chlorides.

Test.—To 5 c.c. urine in test tube add 5 drops concentrated nitric acid and a few drops of 1 per cent. solution of silver nitrate. A slight haze, or no change in solution shows absence of chlorides. May also contain sugar and acetone and sometimes diacetic acid, albumin and hyaline casts.

Three types :—

1. GASTRIC.—Gastric symptoms predominate: vomiting, epigastric pain. Axillary temperature normal; rectal temperature raised.
2. CHOLERAIC.—Sudden onset, diarrhœa resembling true cholera. Rectal temperature 110° F.
3. TRUE HEAT-HYPERPYREXIA.—Nervous symptoms predominate; accounts for 70 per cent. of cases.

Death occurs within a few hours from coma due to respiratory failure. Recovery often followed by relapse. In favourable cases, terminates by crisis and rapid convalescence. Mild cases usually in majority; in them the painful cramps form a valuable diagnostic sign.

Diagnosis and differential diagnosis.—Hyperpyrexia distinctive. Differentiate from uræmia, diabetic coma, alcohol, opium, carbon monoxide and hydrogen sulphide poisoning; may simulate cerebral or pontine hæmorrhage. Diagnosis from cerebral malaria difficult, because heat hyperpyrexia is more common in malarial subjects; rely on enlargement of spleen, history and parasites in blood (these may be scanty). Often mistaken for cerebrospinal fever; distinguish by refractory irregular pupils, strabismus, Kernig's sign, herpes and initial rigor.

Treatment.—In hyperpyrexia if malaria suspected, quinine should be injected intravenously: 7–10 gr. (470–648 mgm.) of quinine dihydrochloride. Every effort must be made to reduce temperature: patient placed on wet sheet, bed cradles or rush-covered bed ("angareeb"—Arabic). Continuous ice-water spray with electric fan stimulates sweating. In Iraq, in second world war, continuous drip saline intravenously gave best results. For convulsions and restlessness: potassium bromide or chloral. Rubbing skin with ice obstructs evaporation and is not recommended. Keep thermometer in rectum and discontinue application of cold at 104° F. (40° C.). If carried beyond this point temperature may sink to 91° F. and dangerous collapse ensue. Patient is then wrapped in dry blanket and stimulants given—tinct. digitalis, min. 40. For convulsions: venesection. For respiratory involvement apply artificial respiration. Lumbar puncture for cerebral cases. Gastric cases: sodi. bicarb., 30 gr. (1·9 gm.), every two hours. During convalescence patient should be shielded from heat, as sweating is not restored for 3 weeks.

Prophylaxis.—Patients in hospital with malaria, typhoid, etc. are especially liable to heat stroke. Suspect those with urinary irritability and suppression of sweat. Salt valuable prophylactic (see below). Heat stroke huts and wards are now provided—air conditioned wherever possible—and methyl chloride or ammonia refrigerating machines employed. Improvised cooling apparatus can be made by filling radiator of lorry with ice and driving fan forcing air by means of a tunnel into a one-bedded bunk. Return to hot climate should be prohibited as otherwise relapse will occur.

Acclimatization.—Now practised in S. Africa for work in mines; candidates are tested in special room at 94° F. (34·5° C.) wet-bulb temperature and then graded according to reactions and ability to sweat. Men born and bred in hot climates do best. Water consumption necessary: in endemic area allowance should be 3 gallons (11·3 litres) of water per man at work, with addition of ½ oz. (15·7 gm.) salt to each gallon (3·7 litres) to counteract hypochloræmia.

LÂTAH.—RUNNING AMOK.—KORO

Name signifies nervous or sensitive state—"*Young-dah-hte.*" Common in Malaya, Java, Dutch E. Indies. Frequently in young women. Psychotic state lasts for years, but does not lead to insanity.

"Lâtah" individual reacts involuntarily to stimuli by irritating words or gestures. During hypnotic state is sensitive to suggestions. High degrees may be followed by swooning and exhaustion. Lâtah individual will imitate pedalling of bicycle till exhausted, etc.; in others, sudden touch or auditory stimulus causing jump or recoil. Hereditary tendency to lâtah in every Malay.

"Amok."—Insensate fury, driving victim to kill without reason—generally brooding upon imaginary grievance—most common in Malays; drugs like Indian hemp (*Cannabis indica*) predispose.

"Koro."—In Macassar, Celebes and S. China; denotes "shrivelling"; feeling of penis retracting into abdomen. Patient may die. Anxiety neurosis, grasps penis and begs for assistance. In anxiety will tie penis to leg, or anchor it by pin. Pathological conditions such as œdema of abdomen, hernia, hydrocele or elephantiasis of scrotum may evoke attack.

Other hysterical states in natives.—"*Banga*" on Congo in women, at puberty, etc.

TROPICAL NEURASTHENIA

Neurasthenia in tropics does not differ essentially from similar condition elsewhere, but is usually more marked and commoner. Tropical conditions provoke manifestations in predisposed individuals. Possibly a certain number go to tropics to escape strain of social life at home. Predisposing causes: chronic malaria, dysentery, etc.; isolation, heat, insect bites, disturbed sleep, proximity to natives with undue appreciation of their psychology. Aggravating factors: absence of seasonal changes, monotony and unpalatability of diet. Tropical heat engenders insomnia which at end of tour causes psychoneurosis. In women menstrual disturbances, parturition changes and anxiety-neurosis are common. Tropical climate is at first exhilarating, but becomes depressing. Hyperglycæmia may possibly be caused by heat: precipitating factor.

Clinical features.—Patient becomes emotional and introspective, with tremors, sweating palms, abdominal sensations, and exaggerated deep reflexes. Sometimes there is divergence of pupil on accommodation (Moebius' sign). Sometimes a suggestion of hyperthyroidism.

Treatment.—Most recover on removal from tropical surroundings, but illness may be prolonged. Remove underlying cause—malaria, for instance, ancylostomiasis, or amœbic dysentery. Holiday in temperate or cool climate. Encourage hobbies and interests. Sedative mixtures, bromides. For insomnia: luminal or allonal.

Prophylaxis.—Subjects of profound neurasthenia should not be permitted to return to tropics: relapse probable. Sometimes recovery may be complete, but at least six months' rest is usually necessary.

PRICKLY HEAT

Miliaria with excessive sweating and principal factor in heat stroke in all tropical climates.

Ætiology.—Mechanism probably depends on cells of stratum corneum which swell and obstruct orifices of sweat glands. Yeasts and mycelium (*Oidium*) frequently in contents, probably secondary invasion. Miliary rash, commonly known as prickly heat, is due to dysfunction of the small sweat glands, and pemphigoid eruption due to similar condition of the large sweat glands and may be associated with heat exhaustion. Four types:—*Miliaria rubra*—papulovesicular dermatitis, connected with hyperhidrosis, may result from few occluded glands in ante-cubital, popliteal fossæ, chest and abdomen. *Miliaria pustulosa*—numerous pustules unassociated with hair follicles. Purulent exudate associated with *Staph. albus*. *Miliaria profunda* associated with tropical anhidrotic asthenia. *Miliaria crystallina* superficial transient rash causing little discomfort.

Clinical features.—Every European liable, especially newcomers. Some never get acclimatized, but disease recurs every year in hot season. Miliaria-like eruption; small vesicles and closely-set red papules—impression of skin sprinkled with grains of sand—mostly on apposing surfaces where subjected to pressure by clothes—under breasts, mid-abdomen, axillæ; sometimes also backs of hands, forehead, scalp; palms escape. Interferes with sleep; may lead to boils. Prickling and itching; provoked by drinking hot fluids. Exposure to sun, close rooms and warm clothing aggravate.

Treatment.—Avoid cause of perspiration, hot fluids, exercise, and especially soap in bath. Mattress and pillows should be covered with grass mat. Punkah or electric fan by night. Afridol soap (oxymercuriotoluylate of sodium) is preventative and curative. Powder body—axillæ and crutch—with astringent powder (equal parts boric acid, zinc oxide and starch). Flannel shirts are better than cotton. To intractable patches apply calamine lotion, or powder of sublimed sulphur 80, magnesia 15, oxide of zinc 5 parts. Recently established that prickly heat is relieved by reducing salt intake so that relapse can be brought about by increasing intake of salt. Relief from symptoms produced by pyribenzamine, a histamine preparation.

Prophylaxis.—Inunction of skin with lanoline once weekly recommended. Also Caladryl ointment.

TROPICAL CHEIROPOMPHOLYX

Vesicular eruption on hands, fingers and feet. Common in Africa and India. Probably eczematous, aggravated by heat. Owing to thickness of horny layer, vesicles remain in skin for days and become secondarily infected. Some forms are caused by external irritants or toxic eruptions due to ringworm.

Treatment.—Calamine and lead lotion with *Liq. picis carbonis.* Also ointment of coal tar, 3, powdered charcoal, 1, zinc oxide, 1, lanoline and petroleum jelly, 12 parts. The ointment is well rubbed in and cotton gloves and socks worn. Resorcin soap is helpful.

CRAW-CRAW. NODULAR DERMATITIS

Papulo-pustular skin affection common in Central Africa, Ceylon, India, S. China. Commences as itching papule which becomes generalized on back, chest, arms. Mostly climatic, but many cases are probably pustular scabies or nodular dermatitis associated with *Onchocerca volvulus.*

Treatment.—Pustules opened, crusts removed, ulcers scraped and dusted with boric acid powder, washed with corrosive sublimate lotion (1: 1,000), covered with absorbent cotton wool and bandage. Penicillin ointment or injections.

CHAPTER IX

MISCELLANEOUS GROUP

AINHUM

Fibrous constriction of toes, especially 5th, sometimes little finger. Rare in women and children, chiefly in adult male natives of E. Indies and other indigines, especially negroes, Africa and America.

Commences as narrow groove in skin on plantar side of little toe, gradually involves circumference, constricted as by ligature ; one or both feet affected. No pain ; toe drops off, or is amputated. Third and fourth toes rarely affected, big toe never, occasionally 5th digit of hand. Osteoporosis and atrophy of bone. Only treatment effective is amputation.

BIG HEEL

Epidemic hypertrophy of os calcis in natives of W. Africa (Gold Coast) and in Formosa in young adult males. Fever, pain, swelling of os calcis and occasionally other tarsal bones.

ONYALAI (Essential Thrombocytopenia)

In natives of E. Africa, Rhodesia, Congo, possibly also in China. Bullous sanguineous vesicles ½–¾ in. (1·25–1·8 cm.) on hard palate and buccal mucosa. Hæmaturia, numbness, tingling and pain ; usually parotitis and mental convusion. Pyrexia 103–104° F. (39·4–40° C.). May be widespread hæmorrhages : epistaxis, subconjunctival hæmorrhages. Death from hæmorrhagic bronchopneumonia. Non-infectious, familial. Blood: great reduction in platelets. Considered to be "essential thrombocytopenia" due to defective nutrition. *Differential diagnosis* from snake bite.

Treatment.—Blood transfusion combined with autohæmotherapy.

TROPICAL EOSINOPHILIA

(Pulmonary Eosinophilosis)

First described as pseudotuberculosis of lungs associated with massive eosinophilia in India; but widely diffused in tropics—India, Africa, China, Philippines, S.U.S.A. Spasmodic bronchitis, leucocytosis of 60,000 with high eosinophilia, up to 90 per cent.—higher than in any disease, except eosinophilic leukæmia. Males affected more commonly than females. Febrile periods with splenomegaly. Acute and chronic types recognized. X-rays show disseminated, discrete, mottlings with average single focus about size of split pea somewhat resembling silicosis.

Ætiology.—Circumstantial evidence of virus occurring in groups, or families, spread by fæces under insanitary conditions. Helminthic allergy suggested by recent work.

Pathology essentially eosinophilic bronchitis and bronchiolitis. Reddish-brown areas scattered on surface of lungs with tubercle-like nodules composed of giant cells and monocytes. In serum cold agglutinins (isoagglutinis) are present in high titre. The disease is usually benign and lasts for years and tends to observe a seasonal incidence. Tropical eosinophilia has to be distinguished from Löffler's syndrome which is an allergic manifestation, resembling tuberculosis, from pulmonary coccidiomycosis, sarcoidosis, and bronchial asthma associated with periarteritis nodosa.

Diagnosis by eosinophilia. Distinguish from parasitic eosinophilia by A.C.T.H., or cortisone, in divided doses in 1–2 weeks. No effect on latter rise of eosinophiles in allergic conditions (Thorn test).

Treatment.—Arsenic in some form or other is specific and reacts quickly to intravenous injections of neoarsphenamine in courses of six doses of 0·15 to 0·45 gm. Mapharside, neohalarsine, acetylarsan (stovarsol) also effective. Benylin expectorant relieves bronchial spasms.

Recent discovery of specific action of hetrazan, 600 mg. daily for 4 days, reduces eosinophilia to normal from 5th day onwards. Pulmonary signs and symptoms also clear up (Danaraj, 1956).

CHIUFA

Gangrenous rectitis. In N. Rhodesia at 200–2,500 ft. Onset : sudden and acute. Circum-anal skin and vulva have white powdery appearance. Generalized pains. T. 104° F. Rectal prolapse ; tenesmus ; rectal distress ; at first no diarrhœa but usually constipation. Later, inflammation spreads to colon and there is then diarrhœa. Similar affection of vagina reported.

ULCUS TROPICUM (Tropical sloughing phagedæna)

A particularly destructive form of ulceration of legs, ear and, rarely, other parts, especially in debilitated natives.

Geographical distribution and epidemiology.—In most tropical countries with hot moist climates ; commonest cause of sickness in W., E. and C. Africa. India, Malaya, Pacific Islands, S. America. Majority of ulcers occur during period of low rainfall and low relative humidity.

Ætiology.—True ætiology obscure ; many organisms in slough, but probably has nutritional basis ; spirochætes common, *Sp. schaudinni*, but true infective agent not isolated; may be ultra-microscopic; but sores have been reproduced by inoculation. Commences at site of previous abrasion—insect bite or scar of healed ulcer, often on yaws gumma, or crushing or bruising injury—on ankle and tibial area especially because most exposed to injury, but may occur on arms or hand. Biochemical deficiencies urged as predisposing cause, but may occur in otherwise healthy Europeans in endemic areas. Hypocalcæmia, low blood sugar and low blood urea. Diet deficiencies, especially protein, B_2 and A predispose. Commonly associated with chronic malaria. Virulence of virus appears increased by continued transmission in susceptible community. In Mohammedan countries liable to occur during Ramadan.

Clinical features.—Commences as papule or bulla with serous sanguinolent contents, pain + and some constitutional disturbance. Bulla ruptures, ashy-grey moist slough involves subcutaneous fascia ; centre liquefies and involves fascia, muscles, periosteum and bone. Generally process is limited and superficial, but in advanced cases joints, tendons and blood vessels are destroyed, necessitating amputation. Frequently also septicæmia and death.

Diagnosis and differential diagnosis.—By appearance, malignant character and punched-out edge. From yaws and syphilitic ulceration, varicose ulcers, oriental sore and veld sore.

Treatment.—Diet essential—fruit, vegetables, limes, oranges, fats and butter (vitamin A). Cod liver oil dressings in early stage ; when localized, excision and skin grafting. When septic and ulcerated, scraping is necessary, followed by swabbing with alcohol and strapping with elastoplast. *Copper sulphate treatment.*—Copper sulphate 1 oz. (31 gm.), glycerin 2 oz. (59·1 c.c.), heated and stirred, acid carbolic 1 drachm (3·55 c.c.) to every oz. of solution. Ulcer is cleansed and solution applied on cotton wool for 2–3 min. Dressing of acriflavin (1 : 1,000) on gauze covered with hot fomentation. Tar treatment much employed in Kenya : ulcer swabbed with eusol, tar spread on lint ; changed every 2–3 days. Small ulcers dressed with iodoform gauze and elastoplast dressing. Sulphonamides recently used in Trinidad. Sulphapyridine 3 gm. (46·2 gr.) daily by mouth, is useful in papular stage, but not in chronic. Sulphonamide paste is effective in cleansing up septic edges. (Sulphonamide P. (B.D.H.) contains 30 per cent. sulphonamide in cod liver oil base.) Penicillin injections in large doses generally recommended. Peri-arterial lumbar sympathectomy has been performed.

LEUCODERMA (Vitiligo)

Atrophied depigmentation areas of skin extremely common in native races ; almost any part of body affected. Patches enlarge peripherally observing certain rough symmetry. Texture and glands of skin unaffected. Generally considered to be a trophoneurosis. Cases with positive W.R. may be syphilitic in origin and improve with antisyphilitic treatment. Popularly mistaken for leprosy. In Calcutta, *Bouchi oil* injections are employed : extracted from seeds of *Psoralia comyfolia.* Injections of 0·05–1 c.c. into patches, number of injections varying with size of patch. Formation of pigment noted after 2–3 weeks.

CHAPTER X

VEGETABLE POISONS

LATHYRISM.—FAVISM

Abyssinia, Algeria and India principally. Nervous manifestations, ataxy, spastic paraplegia, weakness, muscular pains, wherever vetches form main articles of food. Formerly " Khasari "—*Lathyrus sativus*—suspected, but now shown that seeds of *Vicia sativa* var *angustifolia* contain alkaloids—*vicine, divicine.* This vetch found also contaminating wheat in India. Disease reproduced in animals on same diet. Arms and trunk seldom involved, incontinence of urine, sexual impotence common and early; chronic, seldom fatal. Aneurin (vitamin B_1) said to be effective in treatment.

Favism is an allergic manifestation, due to a bean (*Vicia fava*) and gives rise to a condition resembling blackwater fever. Common in Sardinia, Greece and the Mediterranean.

ATRIPLICISM

China. Combination of cutaneous and nervous symptoms. Intoxication by ingestion of leaves of *Atriplex littoralis*, also *A. serrata* or *Chenopodium hybridum.* Skin lesions, light-sensitive—itching of hands, œdema and bullæ, gangrene of finger tips ; cutaneous hæmorrhages. Eyelids cyanotic and œdematous, resembles Raynaud's disease or erythromelalgia.

OTHER POISONS

ACKEE POISONING—VOMITING SICKNESS OF JAMAICA
(ACUTE TOXIC HYPOGLYCÆMIA)

Jamaica (probably other W. Indies), in circumscribed, rural epidemics in cooler months, November to April. Considerable mortality. Usually in children.

Ætiology.—Poisoning by Ackee—fruit of *Blighia sapida*, a common tree. When mature and in good condition, fruit is wholesome, but when injured on ground is poisonous. Immature fruit contains a water-soluble toxin. Water in which fruit is boiled is most toxic. Other vegetable constituents of " bush teas " are also under suspicion.

Two polypeptides, *hypoglycin* A and B, have been extracted and identified from aqueous extract of seeds. Both toxic to laboratory animals producing hypoglycæmia, also characteristic of vomiting sickness and associated with fatty changes in liver and complete absence of glycogen. The toxin produces a temporary enzyme block, inhibiting gluconeogenesis. The condition is in fact an acute toxic hypoglycæmia.

Pathology.—Hyperæmia with petechial hæmorrhages of viscera. Fatty degeneration of liver, kidneys, sometimes pancreas and heart, somewhat resembling yellow fever.

Clinical features.—Vomiting and abdominal pains ; then recovery, but 3–4 hours later cerebral vomiting commences, then convulsions and coma, and death in 12 hours. Convalescence rapid. Mortality 80–90 per cent. T. subnormal, rarely 101° F. (38·3° C.). Respirations rapid (26–30) of Cheyne-Stokes type : pupils dilated.

Treatment.—Prompt emetic ; wash out stomach with weak alcohol during primary vomiting.

Prophylaxis.—When fruit falls to ground only opened pods (ripe fruit) to be used for food. Destroy immature pods.

MANIOC

Manihot aipi (sweet cassava) and *M. utilissima* (bitter cassava). Ground roots eaten as cassava cakes in W. Indies.

Poisoning from failure to remove glucoside and enzyme which, with water, release free hydrocyanic acid. Causes vomiting, abdominal distension and impeded respiration. *Nami* (*Dioscorea hispida*), yams in Philippines, cause similar symptoms.

CORAL PLANT

Jatropha multifida causes colic, cramps, thirst and subnormal temperature. *J. curcas* and *J. glandulifera* in W. Indies ; nuts taste like almonds, known as " physic nuts." *J. gossypifolia*, wild cassava or " belly-ache bush " seeds ; intestinal irritant like croton oil. *J. urens* from same area bears leaves with stinging hairs which cause itching, smarting, flushing of face, swelling of lips and faintness.

JENGHOL POISONING

Java Bean, *Pithecolobium lobatum*, causes renal pain, dysuria, often anuria. Urine shows blood-casts and sharp acid crystals which cause necrosis of urethra, fistulæ and extravasation.

DATURA POISONING

India, Ceylon, S. America.

Seeds of *Datura fastuosa* used for criminal poisoning, sometimes have slight taste Produce coma and unconsciousness ; characteristic seeds seen in fæces and in fatal cases in intestine.

MANCHINEAL POISONING

Hippomane mancinella (Euphorbiaciæ), a big tree (30–50 ft. circumference) in N.S.C. America and W. Indies. Latex contains greenish resin. All parts of tree are toxic, but amount varies with season. Hypersensitive persons who pick fruit contract skin eruption, erythema and vesiculations, toxic dermatitis of genitalia and anus, especially corona penis. Conjunctivitis with photophobia and blepharospasm from entrance of latex into conjunctival sac. When eaten, fruit causes vesiculation of mucosa and diarrhœa with blood and mucus.

Treatment.—Manchineal juice washed off with sea water. Blisters treated as in second-degree burns.

ALCOHOLIC POISONING

Alcoholic poisoning occurs in all native races who have access to spirits ; not usually in British Crown Colonies. Rum (65 per cent. alcohol) in West Indies and S. America. Arrack (55 per cent. alcohol) in India, China and Java. Toddy (fermented sap of various palms) causes intoxication in Pacific Islands, Ceylon and W. Africa, also in S. America the fermented juice of *Agave americana*, " pulque."

GINGER PARALYSIS

Ginger paralysis (Jake paralysis) in Jamaica, South U.S.A. (Carolina and Tennessee). Adulterated Jamaica ginger contains 2 per cent. triorthocresyl phosphate.

Flaccid paralysis of distal muscles of limbs without involvement of sensory nerves ; upper arms involved later ; knee jerks increased, but plantar reflexes abolished. Death-rate small, from respiratory paralysis.

Diagnosis.—Chickens inoculated develop polyneuritis.

OPIUM POISONING

Eating or smoking opium—widespread habit, especially in Chinese—causes pin-point pupils, wasting, inelastic harsh dry skin, extreme lethargy.

CANNABIS INDICA

Hascheesh (*Cannabis sativa*)

Grown in India and Arabia ; leaves powdered, chewed or smoked as *bhang* ; extract of flowers, or *ganga*, causes nervous excitement, and, if persistent, chronic insanity with hallucinations and illusions. Hascheesh, often mixed with *Datura* and *Nux vomica*, consumed by millions in Africa and Asia.

KAWA (Yangona)

Powdered root of *Piperaceæ* mixed with water throughout Polynesia. Formerly masticated by girls—now prohibited—produces excitement with temporary paresis of legs. Chronic intoxication : debility with rough, coarse skin.

BETEL

Leaves of *Piper betel* with lime and areca nut (*Arecha catechu*), commonly chewed in India, Ceylon and Far East, staining mouth, lips and teeth bright red. Flushing of skin, especially face. In Central Africa Kola nut (*Sterculia*) produces similar results.

Cocaine (*Erythroxolon cocoa*) widely used in S. America as stimulant and intoxicant. Dried leaves chewed with lime. Drug addicts become emaciated, cachectic and unreliable.

Flax Darnel (*Lolium linicolum* and *L. temulentum*) causes recurrent epidemics of food poisoning in Aden due to eating wheat from Abyssinia containing poisonous weed, covered by moulds (temuline). Dizziness, headaches, slurred speech, staggering gait, generalized tremors. Diarrhœa sometimes, then coma (*loliismus*).

Catha Edulis or Miraa Poisoning.—Miraa, name of tree, *C. edulis*, indigenous to Africa—leaves and twigs chewed or infused to make " Bushman's tea " or may be smoked. Causes mental disturbance in adults. Alkaloids—*cathine*, *cathinine* and *cathidine*.

MUSTARD OIL POISONING (Epidemic Dropsy)

Resembles œdematous beriberi without paralysis or anæsthesia.

Geographical distribution and epidemiology.—Especially in India, Mauritius, Fiji and wherever Indians are settled. Bad epidemic in India, 1934, especially in famine years during food shortage.

Ætiology.—Predilection for female Hindus in middle and upper classes ; children under puberty less liable ; never in infants ; formerly ascribed to damaged rice, now to mustard oil in preparation of curries. Recent investigation leaves little doubt that oil is contaminated with poppy seeds, *Argemone mexicana*. Also common in wheat and chicken foods : fowls die. Argemone (self-sown seed) is common contaminant of mustard plant ; 25–50 mgm. of active extract of oil reproduces disease. Toxic agent unknown ; formerly thought to be allylisothiocyanate.

Pathology.—Extensive vascular dilatation of deeper layers of skin ; atrophy of myocardium ; capillary dilatations in internal organs, especially omentum. Liver has nutmeg appearance. Vascular outgrowths on skin resemble sarcoids, bleed profusely and are mainly due to changes in blood vessels. Slight secondary anæmia, r.b.c. 3,800,000. Differential count increase in lymphocytes.

Clinical features.—Œdema invariable, usually of legs but may be universal ; very persistent. Pyrexia invariable (99–102° F. : 37·2–38·8° C.), precedes or follows œdema. Diarrhœa and vomiting often, duration 6 weeks. Peripheral neuritis absent. *Exanthem* characteristic, a week after œdema; erythematous on face; rubeolar on trunks and limbs. Vascular nævi with telangiectases may be nodular and bleed profusely, usually form in three weeks; may be sessile or pedunculated: from pea to lemon in size. Disturbances of heart and circulation frequent. Lung signs characteristic—like bronchial spasm. Urine of low specific gravity. Primary glaucoma often present.

Diagnosis.—On history, œdema and peculiar rash. From œdematous beriberi, differentiated by pyrexia and persistence of deep reflexes. From hunger or war œdema, on clinical appearances and estimation of serum albumin.

Treatment.—Egg and milk albumin administered in quantities. Liberal protein diet. Tinct. of ephedra, 20–30 min., with calcium lactate, 10 gr. tabs.

IROKO ALLERGY

A number of dense hardwoods of tropical origins—satin wood, teak and mahogany—are capable of causing allergic action in susceptible persons.

Iroko.—British standard trading name for wood of *Chlorophora excelsa*, "African teak," imported in considerable quantities as substitute for real teak. Wood dust produces irritation of exposed surfaces, marked œdema of face, with ocular irritation and blepharospasm, acute coryza, headaches and pharyngitis. Certain soft woods, especially *Obeche* (*Triplochiton scleroxylon*), also have a bad name.

CATERPILLAR AND OTHER INSECT DERMATITIS

The hairs of species of caterpillar give rise to dermatitis and urticaria. In New Guinea and N. Australia it is the moth *Ochrogaster contraria*. In Israel and the Middle East it is *Traumateto pœa pinivora wilkinsoni* which occurs in the pines in afforestated areas. Scales of adult moths which swarm round lights at night produce urticaria, conjunctivitis and facial œdema. In French Guiana the species is *Hylesia urticans*. In French Equatorial Africa and the Gold Coast a similar species occurs; in Brazil flannel moths (*Anaphe renata*) (*Megalopygidæ*) are well known. In Celebes it is *Scirpophaga innotata* and in Japan large epidemics due to *Euproctis slava* have been recorded. In Ecuador a greenish beetle (*Pæderus ornaticornis*) produces on contact a papulo-vesicular rash, in the same manner as the blistering beetle, *Lytha vesicatoria* or *cantharides*.

BEE AND WASP STINGS

Numerous species in tropics give rise to painful stings and effects, which are allergic, are usually more intense than in temperate countries. In Japan the bites of a parasitic wasp, *Sclerodermus nipponensis*, of which the female is ant-like and wingless, cause epidemics of pale swellings 10 mm. in diameter leading to suppuration and lymphangitis.

DERMATITIS VENENATA

Many plants cause dermatitis, erythematous, vesicular or urticarial. Poison ivy (*Rhus toxicodendron*) ; poison sumac (*R. vernix*) in N.E. U.S.A. ; " poison wood " (*Metopium toxiferum*) in S.W. U.S.A. produce severe dermatitis. Contact with plant is necessary ; venom is *toxicodendrol* in small quantities, 0·001 mgm. Repeated attacks do not confer immunity.

Treatment.—Skin washed with soap and water ; do not apply alcoholic or oily solutions.

Most plants are more irritating when wet. Others causing dermatitis are *Cypripedium*, lady slippers, *Euphorbia* and primroses, Lily and Vanilla bean rashes; in Japan lacquer from *Rhus vernicifera*, and sometimes lacrymation.

Pyrethrum dermatitis in Kenya due to leaves of *Chrysanthemum cinerariæfolium* growing at high altitudes throughout the year—with pyrethrum content of 1–2 per cent. Absorption facilitated by constant sweating. Itching commences at corners of eyes followed by lacrymation.

MUSHROOM POISONING

Poisonous species not recognized by taste ; have agreeable flavour. Dangerous poisoning due to genus *Amanita* (*A. muscaria* and *A. phalloïdes* : death cup). Both common and widely distributed in South U.S.A. and S. Europe. Distinguished by persistence of portions of veil encircling stem and little below the cup. Alkaloid ; *muscarine*, allied to pilocarpine. Atropine forms efficient antidote.

Pathology.—Congestion of internal organs, subpericardial and subpleural hæmorrhages. Liver : intense fatty degeneration and necrosis (as in phosphorus poisoning). Kidney : parenchymatous degeneration of convoluted tubules. Severe and widespread damage in C.N.S. Spores of fungi in fæces.

Clinical features.—*Gastro-intestinal* : nausea, vomiting and diarrhœa. *Choleraic* : violent abdominal pain, nausea, vomiting with choleraic stools. Severe hepatitis with jaundice. Toxic nephritis, anuria. *Nervous* : gastro-intestinal symptoms followed by mental confusion and delirium in fatal cases. *Rapid type* : symptoms within three hours of ingestion. *Delayed type :* (*A. phalloïdes*), 6–15 hours.

Treatment.—Stomach pump as soon as possible. Atropine in large doses, intravenous salines. Large doses of collosal kaolin by mouth absorb muscarin.

CHAPTER XI

ANIMAL POISONS

SNAKES

Venom is secreted by glands, connected by ducts with the poison fangs analogous to parotids in animals. Venom squeezed out into hollow fangs by contraction of temporal muscles.

In Africa " spitting cobras " eject with force for considerable distance. Their venom is amber-coloured, composed of modified proteins. In vipers venom acts on vascular system : in colubrines—cobras and sea-snakes—upon nervous system, causing respiratory paralysis.

Addition of 0·4 per cent. formol and maintenance at 38° C. (100·4° F.) transforms venom into anavenin (analogous to diphtheria anatoxin). Russell's viper venom acts as styptic in hæmophilia. Cobra venom is analgesic and has been employed for relief of pain.

Viperine snakes are distinguished from colubrinæ by smaller size, angular head, sharp, stumpy tail, and vertically erectile maxillæ with enlarged tubular fangs anteriorly.

CLINICAL FEATURES

Colubrine bite.—In cobra-bite : severe pain in part inflamed, œdema ; in one hour patient is dull, apathetic, unable to stand. Then nausea, vomiting, profuse salivation, paralysis of tongue and larynx, and respiratory centre. Recovery is rapid. Pupils contracted. In Australian colubrines bite is not severe, but symptoms appear within 15 minutes : vomiting and cardiac paralysis. Pupils widely dilated, insensitive to light.

Viperine bite (especially Russell's viper).—Bite causes severe pain, rapid and extensive œdema, bloodstained discharge and ecchymoses ; collapse, small, thready pulse, nausea, vomiting and dilated pupils with insensibility. Local condition of wound becomes aggravated : suppuration, sloughing, malignant œdema, hæmorrhages from mucous surfaces—hæmaturia or melæna—and the toxin produces vasomotor paralysis. Bites of rattlesnakes show remarkable local lesions—wound suppurates and may be hæmorrhagic or gangrenous. Mortality about 30 per cent.

TREATMENT

Prompt and vigorous.

1. Prevent absorption of toxins.
2. Neutralize toxic effects.

Ligature round limb immediately above bite—india-rubber band best, or strips of clothing. Local venesection to remove venom locally. Second ligature to obstruct veins distal to arterial ligature. Series of incisions made into vein draining bitten area. Amputation of part above bite is effective when immediate (probably within 2 minutes). Destroy toxins by making free incisions and swabbing wound with strong solution of potassium permanganate or rubbing in crystals. Sucking wound is useless. Carbolic or Lifebuoy soap can detoxicate snake venom. Lifebuoy soap in 5 per cent. solution infiltrated at site of inoculation effective after lapse of 1½ hours, even longer if followed by antivenene. When finger is bitten a tourniquet is applied at base and another above elbow: toe similar, then 5 per cent. soap emulsion in sterile syringe injected, 0·5–1 c.c., at points surrounding bite. 5 c.c. should be given in all and bleeding encouraged by crucial incisions with safety-razor blade.

Serum.—Immunity specific for venom of particular species. *Antivenene* serum effective for all snake venoms (not substantiated). Antivenene (*Naja naia*) prepared against Indian cobra is serviceable against African cobra, but useless against Russell's viper (*Daboia*) and rattlesnake (*Crotalus*). Practical method is to issue antiserum effective against common and most dangerous snakes in country. *Antivenene* is given intravenously as soon after bite as possible, before minimum lethal dose of venom has been absorbed, *i.e.*, within 10 minutes. Mortality in Brazil reduced by antivenene from 25 to 2·5 per cent.

Subsidiary measures.—Keep patient warm. Small doses of alcohol, ammonia or strychnine. Overdosage with alcohol to be avoided. Injections of adrenaline.

POISONOUS LIZARDS

In Mexico and Arizona two species: *Heloderma suspectum* and *H. horridum*, "Gila monsters." Heavy, stout, pink with black scales. Live in desert, store fat in tails. Poison apparatus in lower mandible; venom-secreting submaxillary glands connected with grooved teeth. Cause paralysis, dyspnœa, convulsions, dilated heart, venous congestion, and changes in spinal cord.

Treatment.—General lines as in snake poisoning. No specific.

POISONOUS FISHES

In most tropical waters. Venom conveyed by bite (epithelial cells in mouth), or by sting (barbs on dorsal fin).

Bite.—*Murœna*: powerful teeth capable of inflicting bites causing neuro-cardiac effects. **Sting:** poison liberated when barbs are broken, causes inflammation and tetanic symptoms. Sting-ray (*Scorpœnidœ*): numerous species with rays in Indian Ocean, Pacific and Mediterranean.

Fish poisoning from eating fishes containing toxin is common in tropics; in some instances, at certain seasons, poisonous qualities are acquired after feeding in certain localities.

Barracouta (*Sphyrœna barracuda*) in S. Atlantic when spawning causes toxic gastro-intestinal upset. "Ciguatuera" (*Sphyrœna picuda*), sprats (*Clupeus longiceps*)—"Ceylon sardine" produce collapse, sometimes fatal.

"Death-fish," *Tetrodon hispidus*, in Hawaii, and other species in Japan and Korea, have poison in ovaries and eggs, producing severe gastro-intestinal symptoms. King fish (*Scomberomorus cavalla*), an excellent fish, is occasionally toxic.

CLINICAL FEATURES

Pain extending up limbs, profuse sweats, pallor, dyspnœa, tachycardia, vomiting, diarrhœa, morbilliform and scarlatiniform rash.

TREATMENT

Local injection of 5 per cent. pot. permanganate + 2 per cent. procaine + 1 : 1,000 adrenaline.

For fish poisoning, wash out stomach and give purgatives. Combat shock with hot-water bottles, etc.

Poisonous Shellfish.—In S. Pacific fatal cases of poisoning due to shellfish. *Conus* all adorned with bright-coloured shells. *C. tulipa*, *C. marmoreus*, *C. striatus*, *C. geographicus* and *C. aulicus*. Long tubular proboscis protruded beyond shell and opening into sac containing two rows of hollow teeth. Poison delivered onto wounded surface. Symptoms acute pain, swelling, numbness and paralysis—then drowsiness, coma and death. Incise and bleed. Sometimes fatal in N. Australia, Polynesia and Seychelles.

CORALS & SEA ANEMONES

Corals are formed of a number of cœlenterata and zoöantharia, genus *Actinaria*. Abrasions and cuts on skin cause indolent lesions. Also sea-anemones (in Mediterranean *Hellenopolypus* and *Aktinion*) give rise to "sponge-fishers' disease." "Lassoo"-like tubular cells evert and end in harpoon-like structure ; within few minutes of contact a small blister appears on skin, like that due to cantharides ; irritates, itches and is œdematous.

Treatment.—Apply vinegar and olive oil.

JELLY FISH

Medusæ, genus *Obelia*. Certain *nematocysts* are weapons of offence ; ejecting barbs which have poisonous numbing effect, producing local swelling, urticaria and sometimes shock.

Portuguese man-o-war, *Physalia*, has special stinging apparatus which produces dermatitis and skin irritation.

SEA URCHINS (Echinoidea)

In West Indies, especially Barbados, spiny sea-urchins cause septic lesions from punctures of hands and feet by spines. *Tripneustes esculentus* and *Centrechinus antillarum* also have poisonous ovaries and spawn. Pain, nausea, diarrhœa, migraine, resembling fish allergy ; also produced by Mediterranean species.

Treatment.—Spines are fragile and break off deeply. Wounds dressed with antiseptic. Tetanus antitoxin injected.

SCORPIONS (Arachnida)

Scorpions, common in tropics, sting painfully, but not usually dangerously, except in children. May cause death. N. and S. Africa, W. Indies, Mexico, Korea, Manchuria.

Signs and symptoms.—Local pain, œdema, cramps, sweating, pyrexia, vomiting and convulsions. In Trinidad : glycosuria, hyperglycæmia and pancreatitis reported as sequelæ. Poisonous species—S. Europe and N. Africa—*Euscorpius italicus*, *Buthus maurus* ; in S. Africa *Hodogenes*, *Opisthophthalmus* and *Parabuthus*; in Mexico species of *Centrurus* ; in Brazil, *Tityus servatulus* ; in Manchuria, *Buthus martensi*. Paired poison-glands in postanal segment of tail, jointed and flexible. Venom like cobra, but less toxic.

Treatment.—Incise sting, wash with strong potassium permanganate solution. For pain : liq. ammon. fortis ; injection of novocain and adrenaline.

Severe intoxication.—Antitoxin prepared from venom extracted from dried sting and venom glands, injected into horses ; 5 c.c. prophylactic and curative.

SPIDERS (Araneæ)

All possess poison glands. Genus *Latrodectus* (" widow-spiders ") toxic for man. S. Europe, " malmignatte " (*L. tredecimguttatus*) ; Palestine and Middle East, *L. lugubris* ; New Zealand, *L. hasselti*, " katipo " ; N. and S. America, *L. mactans* and *L. geometricus*. In S. Africa, *L. indistinctus*. In Peru : pruning spider, *Glyptocranium gasteracanthoides* ; in S. Africa, " Kroppie spider " (*L. indistinctus*). S. Europe : *Lycosa tarentula*, " tarantula " ; hysterical disease in Middle Ages—" tarantism." Toxin of poison gland causes powerful hæmolysis ; hæmolysin causes œdema with numbness and urticaria ; nerve pain due to stimulation of myoneural junctions ; rigidity and spasm of abdomen : " board-like," resembling acute abdomen or appendicitis. Sloughing of site of bite may occur. In N. Africa species *Chætopelma olivacea* feared by Arabs and bites give rise to acute inflammation.

Treatment.—Wash out wound with pot. permanganate 1 : 4,000 and give by mouth. Intravenous injection of calcium gluconate (10 c.c. of 10 per cent. solution) relieves pain and muscular spasm. Antiserum used in S. Africa and Argentine.

CENTIPEDES (Myriapoda)

Genus *Scolopendra* widely distributed in tropics ; poison apparatus at base of first pair of appendages in modified jaws. *S. morsitans* : size 6 in. ; venom causes local and general symptoms, local œdema and lymphangitis ; dizziness, headache, vomiting.

Treatment.—Sol. ammonia 1 : 5 ; morphia injections for pain.

TICK PARALYSIS

Dermacentor andersoni, " wood tick " of N. America, in E. States *D. variabilis,* give rise by their bite to peculiar paraplegia in sheep, also in man ; sometimes fatal. Similar condition in S. Africa caused by *Hæmaphysalis cinnabarina, Ixodes pilosus;* in Australia by *I. ricinus* and *I. holocylus.* Epileptiform convulsions in cats and dogs. Poison introduced by tick during haustellation. Wound painful, with œdema, and bleeding + in forcible removal of tick, possibly due to an anti-coagulin. Symptoms suggest infantile paralysis. Quite distinct from rickettsia disease. To prevent onset of paralysis removal of tick must be complete as salivary glands are sources of toxin. Protective serum introduced for treatment of dogs and has been successful in humans.

CHAPTER XII

METAZOAL INFECTIONS

ARTHROPOD, FLY AND LEECH INFECTIONS

ARTHROPODA

ACARINE DERMATOSES

Several species of mite in grain, sugar, copra ; temporary parasites of skin, causing intense irritation like scabies. " Grocer's itch " due to *Glycophagus* in raw sugar ; erythematous rash. " Copra itch," *Tyroglyphus.* " Grain itch," *Pediculoides ventricosus*—cotton seed, beans, etc. Severe pruritis ; papular, urticarial rash. *P. ventricosus* usually parasitic on insects ; abdomen of female swollen with eggs like chigger. Eggs hatch in abdomen, young being small editions of adults.

Nuñez Andrade disease—dermatitis from bites of larvæ of *Neoschöngastia nunezi,* a common parasite of fowls, produce small petechiæ. Hæmatosiphoniasis in Mexico due to another fowl parasite—*Hæmatosiphon inodora* (*Chinche de los gallos*) or the chicken bug.

Harvest mites (*Trombidiidæ*), velvet mites ; adults bright red. Velvet mites predaceous on insects and plants. Larvæ (*microtrombidium* or *leptotrombicula*); " harvest bugs "=larvæ of *Trombicula autumnalis* and Chigger mite of U.S.A. (*Eutrombicula batatas*): 150 μ long; legs and body covered with feathered hairs. Toxins injected by long suctorial tube formed by salivary secretions ; penetrates skin and digests surrounding tissues. Other trombiculæ—transmit rickettsiæ of typhus. Adults known as "money spiders" non-parasitic. Larvæ called " Kedani mites "—*Trombicula akamushi, T. schüffneri, T. deliensis* and *T. hirsti.* Inunction with oil of cajuput, bandaging with subacetate of lead, or copper sulphate gives relief from intense itching. Inunction with *dibutyl phthalate* preventative and also a cure. Different species of harvest bugs in tropics are virulent, especially in Surinam (*Acarus batatus*), New Guinea; Celebes (*Microtrombidium wichmanni*); S. America (*M. molestissimum*) known as "Bicho Colorado."

Demodex folliculorum in hair follicles and sebaceous glands; similar species in domestic animals. Minute (0·3–0·4 mm.); cause seborrhœa and inflammation of Meibomian glands of eyelids. Abdomen separated from cephalothorax, elongated, transversely striated; head with prominent rostrum without eyes; mouth adapted for sucking; cephalothorax with 4 pairs of short, rudimentary claws. To demonstrate: express sebum from sebaceous glands or comedones and examine with microscope in drop of xylol or oil. Lays heart-shaped eggs, 60–80 μ by 40–50 μ.

Sarcoptes scabiei, itch mite, causes scabies, particularly common in tropics; causes pustular rash, especially in lepers, like Norwegian scabies. In W. Africa many cases of "craw craw" are scabies. Similar species in domestic animals, foxes, wolves, jackals and llama.

Females 0·3–0·4 mm., bigger than male (0·2 mm.); sexes distinguished by epimera of second pair of hind legs which unite with sexual orifice in male and are free in female. Suckers on much reduced legs in female, on 1st, 2nd and 4th legs in male. Surface covered with transverse folds and bears number of spines and conical scales. Gravid female lays eggs in skin; eggs measure 150 μ by 100 μ; in 3–5 days give rise to larvæ and nymphs which live like adults and pass through 4 stages in 3 weeks. Nymphs moult, become sexually mature; average life of adult, 4–5 weeks.

Treatment.—Benzyl benzoate (*Proscabin*): lotion of equal parts benzyl benzoate, industrial spirit, soft soap—1½ oz. Treatment in 45 minutes; no damage to skin. Body washed with soft soap in warm bath at 100° F. (38° C.) for 10 minutes and brush. Second bath one day later. Simple treatment, rapid cure.

Rotenone.—Active principle of derris root, non-oily, mucilaginous, with 2 per cent. rotenone. Twice daily for two days.

Tetræthylthiuram monosulphide in 5 per cent. solution rubbed over body, exception face and head, twice daily, cheap, clean, effective.

Gammexane—½ per cent. in ointment is said to be the most efficient remedy yet devised.

CHIGGERS.—Chigger flea (*Tunga penetrans*) important as cause of suffering and invalidism. Imported from S. America to West Indies, W. and S. Africa. More recently to E. Africa and West Coast, India. Somewhat like common flea; 1 mm. long; large head; deeper-brown abdomen. Lives in dry, sandy soil—dust, ashes, stables and poultry yards. Attacks all animals and man. Lives free with male until impregnated; then burrows by mandibles into skin and ovulates; abdomen swells to size of small pea. Epithelial layer of skin becomes attenuated; parasite anchored in burrow by chitinous excrescences; spiracles project through opening. Eggs, when mature, are expelled through hole in skin;

female dies and parts slough away. Larvæ hatch in soil in 3–4 days, pupate on 6th ; imago emerges 17th day. Chigger causes inflammation, suppuration, pea-like elevations, secondarily infected by pyogenic cocci or even by tetanus. Feet commonly infected ; sometimes hands, soles, interdigital spaces, roots of nails. Usually one or two ; may be hundreds.

Treatment.—Remove chiggers as soon as possible. Kill by pricking with needle, chloroform, turpentine or mercury ointment. Enlarge opening by needle and enucleate chigger. Antiseptic dressings.

Prophylaxis.—Floors swept and sprinkled with pyrethrum powder or carbolic acid ; cattle sheds and pigsties treated. Pigs not kept in vicinity of houses. High boots with powdered tobacco inside recommended. Natives prevented from walking in bare feet. Daily inspection of feet, also rubbed with mixture of lysol min. 5 in 1 oz. vaseline ; especially in interdigital clefts.

LINGUATULIDÆ.—Degenerate arachnids with annulated body, roughly resembling tapeworms. *L. serrata*. S. Germany, Switzerland, Brazil. Adult stage in nasal cavity of dogs, wolves, foxes, sheep, goats. Larvæ in mesenteric glands of domestic animals. Occasionally in liver of man. Causes no symptoms. Reported in Brazil as intestinal parasite. Infection contracted by eating raw vegetables contaminated by nasal secretion of dogs.

Body : pear-shaped, flattened, transversely striated with 90 rings. *Male* : white, 18–20 mm. by 3–5 mm. *Female* : 8–10 mm., grey or brown, packed with eggs. Anteriorly, 8–12 mm. broad, posterior 2 mm. Eggs ovoid, 90 by 70 μ. Eggs with embryos deposited by female, pass out with nasal mucus, become attached to grass and ingested by definitive host ; penetrate mucosa and enter viscera. Larva (5–6 mm.) encysts. Ingested by carnivores, escaping from cyst, falls into peritoneal cavity or even lumen of intestine and reaches adult stage in nasal cavity of same host.

Porocephalus armillatus.—Infests negroes in C. Africa ; recorded from Java, Sumatra, Manila and China. Adult form in trachea and lungs of pythons and snakes. Nymphal form in lion, mandrill, giraffe, African hedgehog. Vermiform, yellow, translucent. *Male* : 3–5 cm. with 16 rings. *Female* : 12 cm. with 20 rings. Eggs (80–100 μ) contain well-developed larvæ. Passed with bronchial secretion of snakes, ingested with contaminated food or water by monkeys, sometimes by man. Egg envelope digested by duodenal (not by gastric) juice ; larvæ penetrate intestinal wall and peritoneum, and enter thoracic or abdominal organs, such as liver. Protracted development (1–2 years) ; encyst as nymph. When intermediate host is eaten by snake, nymphs are liberated, and penetrate into lungs, where they develop rapidly into adult form. Many cases found in Belgian Congo within lumen of small intestine and in lungs; intussusception due to larvæ reported; when cretified demonstrated by X-rays.

In Oriental region *P. moniliformis* is parasitic in pythons—more slender, more rings. Two cases from U.S.A. with *P. crotali* of rattlesnake.

Suggested that human infection is acquired from eating snakes, but more probably by drinking water contaminated by snakes.

MYIASIS

Partial parasitism by larvæ of muscid flies. Eggs deposited on wounds or apertures: in others larvæ emerge from hiding places to feed on blood.

NASAL, AURAL, OCULAR MYIASIS

Cochliomyia hominivorax, "screw-worm fly," 9–10 mm. long—America, Canada to Patagonia. Active in heat of day, deposits 300–400 eggs in open wounds, and in nasal cavities. Larvæ, "screw-worms," hatch in a few hours, destroy mucous membrane, periosteum, bone and penetrate brain—fatal. Larvæ white, 19 mm.; twelve segments and circles of spirally arranged spines. Initial symptoms are tickling pains and nasal obstruction. Epistaxis common.

Chrysomyia bezziana.—India and Cochin China, breeds in living tissues producing destruction as above. *Female*: 8 mm. by 13 mm. metallic blue, greenish thorax. *Male*: eyes reddish-brown, approximated. Larvæ 12 mm., yellowish-white with pigmented extremities.

Rhinœstrus purpureus (bot-fly).—"Head maggot." Russia and N. Africa. Deposits eggs near the eye or nose. Habits similar to bot-fly of sheep.

Wohlfahrtia magnifica (Russia and S. Europe).—"Flesh-eating fly"; breeds in living tissues, especially wounds, nasal fossæ, palate and eyes. 10–13 mm.; ashy-grey. Larvæ identified by shape of posterior stigmata.

Ocular myiasis.—In tropical countries larvæ in lids and conjunctival sac. Pass into lachrymal passage, gain entrance into intraocular tissues. Different species: *Rhinœstrus bovis, Hypoderma bovis, Sarcophaga* sp., *Gastrophilus intestinalis* and *G. equi,* also *Œstrus ovis*—bot-fly.

Eye gnats. Family *Chloropidæ* (Hippelates flies) "frit flies."—Small flies with short aristate antennæ, feed on lachrymal secretion, sebaceous material, pus and blood; very persistent; convey spirochætes of jaws. Larvæ in grass (stem maggots). In California *H. flavipes* cause "pink eye." Eye fly of India, Ceylon, Java, *Siphunculina funicola,* is responsible for spread of epidemic conjunctivitis. Seasonal prevalence in Assam coincides with appearance of fly.

SUBCUTANEOUS MYIASIS

Dermatobia cyaniventris.—"Macaw worm," "Ver macaque." Œstrid or bot-fly. S. America; infests cattle, mammals and man. Non-blood-sucking, with primitive mouth parts. Eggs deposited on leaves in damp places, in haunts of mosquito (*Janthinosoma lutzi*) other species and other insects, *e.g.,* flesh flies, stable-flies (Stomoxys) and some species of tick. Packets of eggs in cement softened by moisture adhere to insect thorax and are thus conveyed to man and animals. Larva at early stage has swollen head, elongated tail = *ver macaque,* later larger ovoid = *torcel*, or *berne*, surrounded with transverse row of spines; falls to ground; pupates. Hatches in 2 days, then penetrates skin forming aperture which exudes black fæces. In man in head, arms, back, abdomen, scrotum, thigh, axilla. Pain + when larva is active.

Treatment.—Remove without incision ; larva slips out of aperture widened by forceps.

Cordylobia anthropophaga.—Tumbu fly, " Ver du cayor." Tropical and Central Africa. Flesh-eating fly, 8·5–11·5 mm., yellowish grey, with brown wings ; closely resembles *Auchmeromyia* (male *Cordylobia* distinguished by closely-set eyes). Usually inactive, but rapid flight when disturbed. Eggs laid in soil ; white larvæ, easily visible, search actively for host ; provided with special mouthparts and cuticular spines to aid penetration of skin of forearm, scrotum, upper thigh and buttock. Lesions resemble inflamed tumour ; no suppuration. Larva emerges in 6–7 days. Pupa has square truncated extremity and is found in rat-holes. Metazoal immunity produced by repeated infection of skin of guinea-pigs which eventually become resistant. Immune skin grafts on to non-immune animal retain and impart immunity.

Blood-sucking Fly Larvæ. (*Auchmeromyia luteola*).—" Congo floor maggot." Africa, N. Nigeria to Natal. Adult fly 10–12 mm. stoutly built, orange-buff with numerous black hairs. Large head, separated eyes ; two dark longitudinal stripes on thorax. Second abdominal segment in female twice length of male. Smoky-brown wings with conspicuous venation. Usually sits motionless on thatch beams, cobwebs and walls of native huts ; difficult to see. Eggs deposited in cracks and crevices of mud floor, especially if contaminated by urine.

" Congo floor maggot " 15 mm. is the larva : found under sleeping mats, in crevices and in moist earth to depth of 3 ft. ; emerges to feed on blood at night ; drops off when disturbed. Dirty-white, semi-transparent ; with eleven segments, at posterior part of each of which are three short limbs and transverse spines which enable larvæ to move rapidly. Paired groups of minute teeth form a cupping apparatus on anterior segment. Dorsal diverticulum (food reservoir) opens into œsophagus and forms conspicuous red object after feeding on blood. Pupa : reddish-brown, oblong, 9–10·5 mm. by 4–5 mm. ; pupal stage lasts 2–3 weeks.

INTESTINAL MYIASIS

Residence in intestinal canal is a feature in life history of diptera. Eggs, licked from skin or swallowed in food, hatch in stomach where larvæ develop and appear in fæces and vomit. Ringed, cylindrical, ½–1 in. in length, beset with little spines or hairs. Over 20 species recognized in human fæces. Usually *Fannia canicularis* (small house fly), *F. scalaris*, *Musca domestica* or *Piophila casei* (cheese maggot). In Africa : *Chrysomyia chloropyga* and *C. putoria*.

Occasionally cause abdominal pain, diarrhœa and vomiting.

Treatment.—Expelled by dose of castor oil.

SKIN MYIASIS. LARVA MIGRANS

Common in S. Africa, Ceylon, India, Florida, S. Russia. Multiple gyrating lesions of legs and feet produced by burrowing of larvæ of various arthropods and helminths ; in *tropical form* by larvæ of flies *Hypoderma* and *Gastrophilus*.

In S. Africa ; burrows produced by mite (unidentified) ; resembles *Tetranychus molestissimus*, common also in Argentine and Uruguay. Mite, and eggs, 0·33 mm. in diameter, demonstrated at end of burrow

Multiple lesions in Florida and S. America due to larvæ of nematode, *Ancylostoma caninum*, parasite of dogs and cats ; has been reproduced artificially by these larvæ which live in soil (*see* Ancylostomiasis). Seasonal incidence in summer months after rain. Most cases due to sitting on beach above high water mark. Children most attacked between fingers and toes.

Other larvæ, especially *A. braziliense* of dogs and cats, burrow like mole leaving a red line and a ridge ⅛ in. high ; travel ½–1 in. in 24 hours. Zigzag, twist, do not bifurcate ; as advancing end progresses, opposite fades. Itching +, sometimes bullæ on face, chest, soles of feet, legs.

Visceral *larva migrans* due to species of helminth not adapted to man. In the liver lesions are due to migration of *Toxocara canis* and *T. cati*. Diagnosis can be made from hepatomegaly and constant eosinophilia.

Diagnosis.—By appearance. Lombard's method : epidermis cleared with machine oil ; then binocular dissecting microscope (150 diam.) reveals larva.

Treatment.—Excision of portion of burrow with advancing larva. Refrigeration with ethyl chloride of area 1½ in. at visible end of burrow for 2–4 mins. Rubbing in *oil of chenopodium* also effective. Diathermy advocated ; needle point of apparatus with 1/16 in. spade directed to right spot ; instant relief ; continue for 7 days.

LEECH INFECTION

In jungle and grass land leeches live in abundance and are a great nuisance ; may be dangerous, causing fatal bleeding.

Hæmadipsa zeylanica: 1 in., thickness of knitting needle, clings to leaf or grass, waiting for passing animal or man ; attaches itself to skin and sucks blood ; may cause intractable sore. Occasionally invades nares or pharynx. Severe headache, epistaxis.

Remove by salt-water douche. Protect feet and legs properly in passing through jungle.

In S. Europe and N. Africa the horse leech (*Limnatis nilotica*) enters gullet and nostril and produces haemorrhage and may cause suffocation.

CHAPTER XIII

METAZOAL DISEASES: HELMINTHIC INFECTIONS

TREMATODES

FASCIOLIASIS

Fasciola hepatica, parasite of liver rot in sheep.—Over 150 cases in man, probably quite common; Cuba, Venezuela, Argentine, Central Europe, Greece, England. Found in portal vein and subcutaneous abscesses, usually causes little disturbance, possibly cirrhosis of liver. In Syria: epileptiform fits associated with buccopharyngeal infection—" halzoun."

Typical trematode, leaf-shaped, 2–3 cm. by 8–13 mm. Anterior extremity narrow, containing oral sucker; ventral sucker larger, 3 mm. from anterior extremity. Branched intestinal cæca with diverticula. Egg (found in fæces) operculated, 140 μ by 90 μ ovoid, brown-bile-stained. Ciliated miracidium develops in eggs, 2–3 weeks, enters freshwater snails, *Limnæa truncatula* (Europe), *L. pervia* (Japan), *L. vicetrix* (Cuba), becomes sporocyst, daughter sporocysts, rediæ, then cercariæ in 2 months. Cercaria: blunt-tailed, settles on grass, secretes mucus to form cysts; then as metacercaria eaten by host. Human infection contracted by eating watercress in meadows frequented by sheep.

Treatment.—None really effective. Emetine injections, 10–12 gr., in separate courses; also big doses of mag. sulph. with intravenous neostibosan.

Fasciolopsis buski, normally parasite of pig, reservoir for man.—China, India (Assam), Malaya, Sumatra, Borneo. In Assam 50 per cent. infested; only small number show symptoms.

Resembles *F. hepatica*, but larger; found in small intestine, rarely in stomach. Flesh-coloured, elongated, oval, 3 cm. by 12 mm. Transverse row of spines, numerous near ventral sucker, which is larger, close to oral. Intestinal cæca simple with two characteristic curves towards mid-line. Egg operculated, 130 μ by 80 μ, yellow, numerous in fæces. In water forms in 3 weeks a ciliated miracidium which develops in fresh-water snails—*Planorbis cœnosus*, *P. schmackeri*, *P. hemisphærula*—sporocyst in 3 days. Rediæ, daughter rediæ, cercariæ (whole cycle, 2 months). Cercaria, short-lived, lophocercous (membranous tailed), well-developed digestive tract, encysts as *metacercaria* on fresh-water plants—water-calthrop (ling), *Trapa natans* (China), *T. bicornis* (India), also *Spirodela polyrhiza*. Metacercariæ adhere to outer skin of ling and are torn off by teeth. Plants grown in ponds are fertilized by human fæces; therefore *F. buski* limited to distribution of plants. Cysts taken into mouth, pass through stomach, excyst in duodenum, become attached to intestinal wall.

Clinical features.—1–2,000 flukes often in small intestine, causing alternate diarrhœa and constipation. Fæces offensive, pale yellow.

Œdema of face, abdominal wall, genitalia and legs; sometimes ascites. Discomfort may simulate duodenal ulcer. Death from exhaustion rare.

Treatment.—β naphthol, gr. 10; oil of eucalyptus, min. 3; tetrachlorethylene, ʒ i; hexyl-resorcinol, 0·4 gm. for child under seven, 1 gm. from 13 upwards: all effective.

CLONORCHIASIS

Biliary and hepatic disease caused by *Clonorchis sinensis*.

Geographical distribution and pidemeiology.—Disease of Far East, India, Mauritius, Japan, Korea, Formosa, Indo- and S. China. Recently new area on Pacific Coast of America and California. In fish-raising provinces in China 50–67 per cent. of native population affected.

Ætiology.—*Clonorchis sinensis* inhabits biliary passages of man, dog, cat, pig, rat, mouse, badger, camel. Usually in adult man. May invade pancreas and ducts, rarely duodenum, never gall-bladder.

Spatulate fluke, 10–20 mm. by 2·5 mm. Cuticle has no spines; oral sucker is larger than ventral. Intestinal cæca are simple. Genital pore in mid-line in front of ventral sucker. Testes branched in posterior part of body. Cross-fertilization, as in other members of group. Sperms enter female opening of genital pore, pass through uterus to spermatheca.

Egg: 28–30 μ by 15–17 μ, operculated, contains miracidium and has terminal spine resembling miniature electric light bulb; susceptible to desiccation, killed by decomposition; viable in water 5 weeks; ingested by snail before escape of miracidium, which has life span of 20 minutes. Development in *Bithynia* (*Parafossarulus*) *striatula* (Japan, Korea, Formosa); *B. fuschsiana* and *B. longicornis*, and *Melania hongkongiensis* (China). Miracidium pierces œsophagus, casts cilia and becomes sporocyst; later, elongated rediæ pass into peri-œsophageal sinus and move tailwards into liver within 3 weeks. Cercariæ: two pigmented eye spots, blunt tail, emerge into water where, within 24–48 hours, they encyst as metacercariæ in muscles and under scales of freshwater fish, *e.g.*, Cyprinidæ, Anabantidæ; 34 species susceptible. Cercarial glands have, histolytic secretion dissolving skin. Metacercaria secretes viscous fluid forming inner cyst; is then encapsulated by fibrous layer in fish, then eaten half raw or pickled in *soy sauce*.

Adolescercaria.—Fully developed cyst, protective capsule against gastric juice withstands temperature of 50–70° C. for 15 minutes. Cyst wall digested by succus entericus in duodenum near papilla of Vater. Adolescercariæ escape, attach themselves to mucosa and attain maturity in 26 days. By chemotaxis a small proportion reach bile ducts. Egg production very large—200–400 daily; 21,000 flukes may be found at autopsy. Life-span, 12 years.

Pathology.—*C. sinensis* thickens biliary canals, passes into cavities and diverticula communicating with bile ducts which contain large number of flukes. Liver is enlarged and cirrhotic; spleen hypertrophied ; intestine shows chronic catarrh. Sometimes found in pancreas, duodenum and stomach, causing ascites and anasarca. Carcinoma may ensue. Death from cirrhosis of liver.

Clinical features.—Enlargement of liver, chronic diarrhœa, recurring icterus, anasarca, cachexia fatal in several years. In mild infections : epigastric distress and night blindness.

Diagnosis.—Obscure hepatic disease from Far East suggests *C. sinensis.* Eggs in fæces. Leucocytosis 30,000 ; eosinophilia 40 per cent. Eggs demonstrated in duodenal juice by duodenal sound.

Treatment.—Unsatisfactory. Intravenous Fouadin (trivalent antimony), 1·5–5 c.c. ; 10 or more injections. Gentian violet, malachite green and Nile blue all lethal to clonorchis, but dosage not satisfactorily settled ; also these dyes have toxic action on man. Continuous non-surgical drainage of bile by duodenal tube (cocainizing throat to prevent vomiting) gets rid of many clonorchis eggs and toxic matter, and is beneficial as temporary measure.

OTHER FLUKES OF LESS IMPORTANCE

Opisthorchis felineus.—Inhabits liver and bile ducts. Common in man in E. Prussia, Siberia, Annam, Philippines ; also in dog, cat, glutton, pig. Fluke 8–11 mm. by 1·5–2 mm. Egg operculate, yellow-brown, 30 μ by 12 μ. Intermediary: snail, *Bithynia leachi.* Development as in clonorchis ; metacercariæ in tench (*Tinca tinca*) and chub (*Idus melanotus*). Behaves in man as clonorchis, but is not specially pathogenic ; 200 or more may be found at autopsy.

Heterophyes heterophyes.—In small intestine in large numbers ; common in man in Egypt, China, Japan ; also in fox, dog, wolf, cat.

Minute, pyriform, 1–1·7 mm. by 0·3–0·7 mm., grey ; uterus showing as brown patch in centre ; ventral sucker three times size of oral ; muscular ring armed with teeth ; cuticle thickly set with quadrate scales. Egg, 20–30 μ by 15–17 μ, light brown, contains ciliated miracidium, develops in brackish-water snails—*Melania tuberculata, Cleopatra bulimoides* and, in Egypt, *Pironella conica.* Cercaria, with eyes, lophocercous. Metacercaria in mullet (*Mugil cephalus*), minnow (*Gambusia affinis*). Produce infection when eaten improperly cooked ; other species recognized : *H. brevicæca,* and *H. taihokui* and, in Japan, *H. katsuradai,* stouter species.

Clinical features and treatment.—Imparts coffee-ground appearance to intestinal wall. Enormous numbers adherent to small intestine. May give rise to diarrhœa. Eggs found in intestinal wall and myocardium. Claimed in Manila that it gives rise to symptoms resembling cardiac beriberi. Readily removed by thymol, 60 gr., or oleoresin of aspidium, 60 min.

Metagonimus yokogawai.—Very common in Far East, Korea, Japan, Formosa and Balkan States. In upper small intestine of man, cat, dog, pelican.

Smallest fluke in man, 1·1 mm. by 0·42–0·7 mm. ; cuticle covered with small spines ; ventral sucker displaced to left, otherwise resembles above. Eggs, 33 μ by 21 μ, regularly ovoid. Develops in *Melania libertina* and *M. ebenina*. Cercariæ : lophocercous, anterior end armed. Metacercaria encyst under scales of fish—*Plecoglossus altivelis* —eaten raw by Japanese.

Clinical features.—Probably causes catarrh and diarrhœa.

Treatment.—As for *H. heterophyes*.

Echinostoma lindoensis.—Philippines and Celebes (Lake Lindoe). Typical echinostome with spines round anterior sucker. In large numbers in jejunum, causing diarrhœa, abdominal pain, slight eosinophilia. Develops in two intermediary snails : *Anisus sarasinorum* and *A. convexiusculus;* metacercariæ in mussels—*Corbicula lindoensis, C. subplanata*.

E. ilocanum and *E. malayanum*, in Malaya. Natural host, pig, snail host.—*Gyraulus prashadi*. *E. jassyensis* in Rumania, *E. recurvatum* in Java ; and *E. surfartyfex* in Assam.

Dicrocœlium dendriticum (*D. lanceatum*). Normal host sheep, found in biliary tract of man, Germany, Italy, France, Egypt, China. Eggs passed in fæces, do not hatch in water, ingested by land snails—*Zebrina detrita, Helicella candidula, H. itala, Torquilla frumentum, Cochlicella acita* and others. *Plagiorchis javanensis* in intestine of Javanese—together with *E. ilocanum*—normal host, amphibia and bats, develops in snail—*Stagnicola emarginata angulata*.

Treatment.—Efficacious : *Filix mas*, min. 90 ; trichlor- or tetrachlorethylene, min. 40–60.

PARAGONIMIASIS : LUNG FLUKE

Paragonimus ringeri, *P. westermani*, and allied species (lung flukes), in lungs of man, dog, wolf, leopard, cat, mink, pig, otter, ichneumon. Produce lung disease associated with hæmoptysis.

Geographical distribution and epidemiology.—China, India, Japan, Korea, Philippines; recently also in U.S.A. and West Africa.

Ætiology.—*P. ringeri*, *P. westermani* and *P. compactus*, commonest species in man, show minor distinctions. 8–20 mm. by 5–9 mm., oval, reddish-brown, round in section, ventral sucker larger and anterior to centre of body. Intestinal cæca run zigzag course ; body bisected by large excretory vesicle. Cuticle studded with wedge-shaped spines. Operculated eggs in sputum, 90 μ by 55 μ, with thickening at pole opposite operculum.

Life history complicated. Eggs, voided into cystic pockets in lungs, escape in sputum and fæces ; ciliated miracidium hatches in 4–7 weeks and enters snails : *Melania tuberculata* (Japan, China), *M. libertina* (Korea), *M. obliquegranulosa* (Formosa) ; also other species. In snail forms sporocyst, rediæ and cercariæ (with knob-like tail and anterior stylet). Metacercariæ in various fresh-water crabs—*Potamon obtusipes, P. dehaani, P. sinensis, Sasarma dehaani, Eriocheir japonicus, Cambaroides similis* (Korea). Metacercariæ in liver, muscles and gills of crab eaten raw by man ;

enters his stomach, where the cyst wall is digested. *Adolescercaria* emerges, traverses abdominal cavity, penetrates pleura, reaches bronchioles, forms cystic cavities and becomes adult which can remain viable in the human body 20 years or longer.

Pathology.—Small brown spots in lungs ; scattered burrows towards periphery ; areas the size of a filbert nut, each with 2 or more flukes ; 13,000 eggs coughed up every day. Often associated with T.B. Also found in liver, intestine, skin, testes, muscles and brain (where it forms tunnelled tumours). Eggs in fæces and spinal cord ; may give rise to transverse myelitis. Hundred flukes found in psoas abscess.

Clinical features.—Insidious onset, chronic cough, distress in chest. Abundant brown pneumonic sputum, containing numbers of brown, thick-shelled, operculated eggs ; irregular hæmoptysis. Clubbed fingers ; lungs show hyper-resonance, râles and rhonchi. Abdominal symptoms : dull pains and diarrhœa ; enlargement of liver ; appendicitis ; adenitis ; prostatic enlargement and epididymitis often. Cerebral symptoms : especially in children, Jacksonian epilepsy, hemiplegia, aphasia, visual disturbances. Cutaneous ulceration sometimes.

Diagnosis.—Eggs and Charcot-Leyden crystals in sputum and fæces. T.B. may co-exist. Eggs to be differentiated from *Schistosoma japonicum*. Blood: leucocytosis, 15,000 (no eosinophilia). X-rays (lipiodol) not conclusive, opacities and infiltration sometimes seen. Complement fixation test (extract of *Paragonimus* as antigen) sometimes employed.

Treatment.—Unsatisfactory. Emetine intramuscularly, 1 gr. for 7 days, in courses. Intramuscular sulphonamides have been favourably reported on. Improvement follows lipiodol injections into bronchi.

Prophylaxis.—Destroy sputum and fæces of infected patients. Prohibit sale of crabs which carry parasite. Educational methods.

SCHISTOSOMIASIS (Bilharziasis)

Groups of diseases widespread in tropics and subtropics. Unisexual (sexes separate)—trematodes inhabiting lumen of veins. Three species in man: (1) *Schistosoma hæmatobium*, (2) *S. mansoni*, (3) *S. japonicum*.

(1) URINARY SCHISTOSOMIASIS (*Schistosoma hæmatobium*)
(*Bilharzia hæmatobia*)

Epidemiology.—Great antiquity in Egypt ; eggs found in mummies of First Dynasty. Widespread in Egypt now, in Delta 60 per cent. are infected with *S. hæmatobium* and *S. mansoni*. In Northern Nile Valley, Cairo-Assiut, *S. hæmatobium*, 50 per cent. : *S. mansoni* absent. Heavy infection associated with perennial irrigation, with alternate drying and flushing. Where 5 per cent. population infected 1 : 1,000 die ; where 60 per cent. 1 : 22.

S. hæmatobium.—Found in Africa (Cape especially); isolated foci in Portugal, Corsica, Cyprus, Palestine, Arabia, Madagascar, Reunion, Iraq; imported in 1901 into Perth, W. Australia (has now died out). Recent discovery of endemic focus in Bombay State at Gimvi in the Ratnagiri district, near the Korkan Coast. Species of adult schistosome uncertain. Cercariæ found in *Ferrissia tenuis*, an ancylid snail.

Habitat.—Veins (mesenteric, portal, vesico-prostatic, pelvic, uterine plexus, vesical, occasionally vena cava, pulmonary); 300 or more found at autopsy in submucosa of bladder. *S. hæmatobium* long-lived (20–37 years), may produce carcinomatous changes. Sexes live apart at first; when mature, female enters gynæcophoric canal of male. Experimentally rats, mice, guinea-pigs, monkeys, hamsters and hedgehogs susceptible.

Male.—1·5 cm. by 1 mm., white, cylindroid, outer surface beset with tuberculations. Larger oral and ventral suckers closely situated. Ventral infolding of male forms gynæcophoric canal containing female. Delicate spines on suckers. Four to five testes posterior and dorsal to ventral sucker. Progresses along veins carrying female.

Female.—2 cm. by 0·25 mm., darker in colour, filiform; middle portion in gynæcophoric canal, anterior free. Body smooth, papillæ on posterior end. Ovary and yolk glands anterior to intestinal cæca; genital pore median posterior to ventral sucker; anterior part of uterus contains terminal spined eggs. Genital openings of both sexes face each other. In both sexes alimentary canal commences at prehensile oral sucker; œsophagus, with two dilatations, bifurcates in front of ventral sucker to form intestinal cæca, uniting again into median trunk.

Egg.—Oval, 150 μ by 60 μ; short, stout terminal spine, contains ciliated *miracidium*, head towards blunt end, active so it can turn about. Egg shell permeable to antimony salts. Eggs of *S. hæmatobium* often in fæces, especially in Upper Egypt and Congo (see also *S. intercalatum*). Also in lungs, brain, spinal cord.

Miracidium.—In contact with water, shell enlarges, becomes softened by lytic ferment and bursts by transverse rupture liberating miracidium. Egg remains alive in sterile urine or moist fæces, 2–3 weeks. Miracidium remains active in water for 24 hours; has anterior papillary beak, swims by cilia and muscular action. Has primitive alimentary canal, two cephalic salivary glands, excretory tubules and flame cells.

Process of escape of eggs from tissues.—Paired worms travel to narrowest point. Female leaves male, penetrates into venules, deposits eggs and retracts, so that spine of egg engages vein walls and escapes into tissues. Others think that spine facilitates adherence of ova to vessel wall. The ovum plays a passive part, but endothelial lining is the active factor, only ova laid in blood vessels close to the bladder pass to outside, whilst others are held in the tissues.

Development (on general lines applicable to all three species).—Miracidia penetrate air sac and tentacles of snail of genus *Bulinus* (several species) ; papilla bores in. If heavily infected, snail dies. Cilia cast, penetrates liver (hermaphrodite or digestive gland) *via* lymph spaces. Infection only in warm season (Egypt). Liver of snail turgid, swollen, yellow or orange ; infected individual snails can thus be recognized. Elongated thin-walled sporocyst produces daughter sporocysts, which penetrate gland. Developmental cycle occupies 6 weeks : under optimal conditions a single miracidium produces 100,000–250,000 cercariæ.

Schistosome cercariæ.—Bifid-tailed cercariæ formed within sporocysts ; then escape. Diurnal discharge from pulmonary cavity of snail. Cast off tail on entering skin of host (man). Penetration aided by acid secretion of glands. Most die in transit. Three hundred may enter mouse and only 20 adults develop. Cercariæ adhere to body of host by ventral sucker ; therefore penetrate mucous membrane, mouth or œsophagus ; women and children in Egypt infected by drinking as well as by Mohammedan ceremonial of cleansing mouth with water. In bathing, movement of water attracts cercariæ to skin. Entry causes dermatitis.

Body elongated, forked tail ; 0·48 mm. Head and tail approximately equal length. Cuticle with spines anterior (oral) ; median muscular ventral sucker ; anterior sucker larger than ventral. Central part occupied by circumoral glands—conspicuous, peri-acetabular, opening by ducts on rectractile papillæ surrounding mouth, which is small, oval and anterior. Five peri-acetabular glands with conspicuous nuclei; acidophil. Cercariæ phototactic, emerging from snail 9 a.m. to 2 p.m.; no emergence on dark days. 50–1,000 daily; optimum temperature 32–33° C. (89·6–91·4° F.) (for *S. mansoni* 15–35° C. ; 59–95° F.). Abundant oxygen necessary ; cannot feed ; swims with ease in water, circular movement, propelling towards tail. Rests with tail prongs on surface, slowly sinks, absorbs oxygen through tail, then rises again. Life span : 48 hours ; most active for 24, more so when water disturbed. Warmth is chief factor in attraction to host. Infection by cercariæ easy in laboratory ; insert tail of mouse in water containing cercariæ.

On entry loses cephalic glands ; becomes *schistosomulum*, and adult in portal vein in 6 weeks, travels *via* bloodstream, veins, heart, lungs, some through pulmonary capillaries, some even to skin, causing secondary skin reactions, *e.g.*, urticaria. When mature, pairs in portal vein, goes back against stream to mesenteric veins ; eggs are carried back and deposited in liver and spleen. Discharge of digestive products causes fibrosis, and black pigment from digested r.b.c. : pigment like that of malaria.

No general agreement on differential details of structure in cercariæ of the three human species ; average 0·4–0·5 mm. ; probably individual differences in different batches ; on the whole, cercaria of *S. japonicum* is smaller. All have 5 pairs of salivary-mucin periacetabular glands. (This account is applicable to other human cercariæ.)

N.B.—Innumerable trematode cercariæ in freshwater snails in tropics. Life history of many unknown. All schistosome cercariæ of man, mammals and birds have forked tails.

Cercarial dermatitis produced by entrance of cercariæ into skin (in human schistosomiasis); also by penetration of other species—*e.g.*, " swimmers' itch "—emerging from *Limnæa*, the common pond snail. *Cercaria elvæ* in Lake Michigan, *C. ocellata* in Lake Roath, S. Wales (probably Bilharziella of water birds). In Malaya and India, blotchy papular rash with central punctures produced by cercariæ of *S. spindale* of water buffalo.

Intermediary molluscan hosts.—*Bulinus contortus*, *B. dybowski* (Egypt) *B. innesi* (Sudan), *B. truncatus* (Palestine), *B.* (*Pyrgophysa*) *forskali* (Mauritius, N. Nigeria, Kenya), *B. globosus* (Sierra Leone, Nyasaland), *B. africanus* (Natal), *Isodora ovoidea* (Zanzibar), *Physopsis nasuta* (Kenya). (Exception: *Planorbis* (*Biomphalaria*) *dufouri*, Portugal and Morocco; *Melania nodocincta*, *M. tuberculata*, Nyasaland.)

Development in snails vicarious. *B. forskali* cannot be infected in the Belgian Congo, but is the chief vector in N. Nigeria.

Genus Bulinus: spiral snails, non-operculate, opening sinistral, body contains red hæmoglobin pigment. (Some conchologists recognize three species—*contortus*, *dybowski*, *innesi*—as subvarieties of *B. truncatus*.)

S. INTERCALATUM (*Bilharzia intercalata*)

Variety from Upper Congo, close to *S. hæmatobium*, but resembles *S. bovis*; differentiated by egg, found only in fæces. *Egg*, 140–240 μ by 58–85 μ; spine longer, 20 μ, spindle-shaped, resemble those of *S. mattheei* or *S. bovis*; great variation in shape and size. "Spinster" females often in small numbers. Intermediary snails: *Bulinus africanus*. *B. globosus*.

Pathology.—At first injection of mucosal vessels of urinary bladder; then papules; eggs in blood vessels; trigone usually first affected; granular phosphatic deposit ("sandy patches"); clusters of eggs, principally in submucosa, some calcified. Polypoid excrescences; adeno-papillomata frequently contain adult schistosomes. Nodules of subperitoneal surface may resemble T.B. Muscular coats of bladder hypertrophied, capacity diminished, mucosa covered with blood-stained mucus +, eggs in large numbers. Then phosphatic gravel or stones appear in lacunæ in bladder wall, or free in cavity.

Usually lower end of ureter is affected and sometimes renal pelvis; secondary *hydronephrosis* common (important). Blockage of ureter with calculi common. Hyperplasia of prostate due to eggs. Secondary ascending infection of urinary tract—pyelitis, renal abscess, etc.—and vesiculæ seminales, vaginal wall, cervix; hypertrophy of glans penis, with urethral blockage. Eggs demonstrated by digesting tissues in 3 per cent. potash solution. Found in small numbers in liver, gallstones, heart, kidneys, lungs, brain, spinal cord; sometimes form tumours of peritoneum and uterine ligaments.

Clinical features.—Symptoms vary; great majority mild. Hæmaturia almost invariable; Egyptian peasants regard it as a sign of puberty. In hyperinfection, urinary sepsis and death. Incubation period of disease : 3 months to 2½ years ; 3 periods : 1. Invasion, 2. Deposition, 3. Terminal.

Period of invasion.—Cercarial dermatitis on infection : blotchy papular rash ; severe itching.

Invasion stage.—Pyrexia, urticaria, abdominal pain, high eosinophilia (*see* p. 200).

Deposition stage.—Polyuria, aggravated by exercise, with terminal hæmaturia. Blood clots, sometimes containing eggs, deposited on standing in conical glass. Dull sense of suprapubic oppression ; deep-seated perineal pain ; scalding on micturition. Cystitis with pain, often septic. Sometimes adult worms passed in urine. Frequency often, rectal pain, sometimes with blood and mucus containing *S. hæmatobium* eggs (or double infection with *S. mansoni*). Lasts for months or years. Spontaneous recovery rare.

Terminal stage.—Eggs form nuclei for phosphatic calculi ; symptoms of vesical or ureteric calculus ; dilatation of ureters with hydronephrosis ; superimposed carcinomatous changes may cause exacerbation of symptoms. Hypertrophic contraction, or dilatation, of bladder, hæmaturia +. Involvement of prostate and vesiculæ seminales ; spermatorrhœa, secondary infections (streptococcal) common. Anæmia, hectic fever, debility, death. *Urinary fistulæ* on perineum or posterior surface scrotum caused by infiltration of eggs. In urethra stricture results. Schistosomiasis of spermatic cord and epididymis (tunica and testes seldom). Cord nodular: " bilharzial rosary." Primary schistosome disease of gall-bladder rare. Sometimes bilharzial appendicitis ; in N. Nigeria 57 per cent. of appendix cases in natives are bilharzial. Vaginitis and cervicitis ; papillary growths and ulcers like carcinomata ; papillomata in vagina, round anus and perineum, to be distinguished from venereal warts. Eggs in lungs cause interstitial pneumonia, and arterial changes resembling "Ayerza's disease" ; in brain and spinal cord cause epileptic attacks ; occasionally transverse myelitis.

Diagnosis.—Eggs in urine, especially terminal portion, demonstrated by deposition in urine glass or centrifugation. When scanty, diagnosis is difficult : character of deposit, mucus +, phosphatic crystals, pus cells, bladder epithelium, eosinophiles usually ++.

Cystoscopy.—Examine shreds of mucus for eggs. Appearances of mucous membrane of bladder, especially in trigone : sparse, grey discrete elevations round ureteric orifice ; later hæmorrhagic areas with surrounding hyperæmia. In advanced cases, ridges like " sea-sand " together with papillomata.

Complement-fixation reactions.—Performed as for W.R. Antigen prepared from liver of snails (*Biomphalaria*) infected with *S. mansoni* cercariæ. Group reaction equally effective with *S. hæmatobium*, *S. spindale* and *Fasciola hepatica*. Best results in early infections before deposition of ova; less specific in later cases.

(Antigen prepared by macerating infected snail livers in absolute alcohol, filtered and evaporated by Sprengel's pump; saline extract made.)

Intradermal test.—Similar to Casoni reaction (*see* p. 240). A saline extract (*vide* above) of livers of *Pl. exustus* infected with *S. spindale*, filtered, made bacteria-free and injected intradermally (4 minims). Positive reaction immediate : wheal, zone of erythema with outrunners. Delayed reaction : 5–18 hours. Diagnostic for schistosome group ; persists for years after cure.

Differential diagnosis.—From vesical calculus, T.B. cystitis, renal calculus, all other forms of hæmaturia, filarial hæmatochyluria, gonorrhœal cystitis, prostatic disease.

Treatment.—Intravenous injections of sodium-antimony-tartrate. (Tartar emetic.) Schistosome adult affected by antimony, especially ovary; cercariæ and miracidia less so. Prevents hatching of eggs in water; eggs become dark and shrivelled after 10 gr. of antimony tartrate.

1. *Sodium-antimony-tartrate:* intravenous injection alternate days, for 4–6 weeks, commencing with ½ gr. in 10 c.c. of distilled water ; increase by ½ gr. to maximum (for adults) 2½ gr. Total dosage : 25–30 gr. Toxic phenomena avoided by addition of 5 per cent. glucose. Rapid improvement ; eggs and blood disappear after 15 gr. For children under 10, dose of 0·1 gr. is sufficient ; maximum 1 gr. If course is interrupted, must be recommenced *ab initio*. Toxic effects : coughing, retching, vomiting, flushing. More severe antimony reaction : headache, arthritic pains in shoulder joints. *Pentavalent compounds of antimony not effective.*

2. *Fouadin* (13 per cent. trivalent antimony compound—antimony pyrocatechin-disulphonate of soda). Used in Egypt ; cure in 19 days ; in over 90 per cent. (1930) ; more rapid than (1). Preferably intramuscularly into buttock ; or intravenously in 7 per cent. solution : dosage 1·5–5 c.c. : one dose of 1·5 c.c., one 3·5 c.c., 7 of 5 c.c. ; total of 9 injections ; maximum 15. Average quantity of antimony 0·4 gm., excreted in urine and fæces. Late vomiting sometimes. No severe local reaction at site of injection. Sometimes toxic necrosis of liver follows with death. Intravenous injections satisfactory on alternate days. Used in S. Africa for children.

3. *Anthiomaline* (antimony thiomalate of lithium) now considered better than tartar emetic (in ampoules : 6 per cent. solution, 10 per cent. antimony). Total necessary : 50 c.c. (or 0·3 gm. metallic antimony). Intravenous : 0·5 c.c. for children ; 1·5 c.c. for adults ; maximum 4 c.c. Intramuscularly : 12 injections on alternate days (one of 1·5 c.c., one of 3 and 10 of 4·25 c.c. ; total 47 c.c.). Living ova not passed after 21·5 c.c. Local reaction (pain) sometimes ; general reaction negligible.

4. *Emetine hydrochloride.* Toxic to schistosomes. Given intravenously, but not recommended on account of toxic action; useful

for those resistant to antimony: ½ gr. in solution; maximum for child, 1 gr.; total 15 gr. Adults 1½ gr. daily; total 20 gr. Intramuscularly less effective.

5. *Miracil D.* (hydrochloride of 1-methyl-4-beta-diethyl-aminoethyl, aminothioxanthone or *lucanthone*) in tablets, each of 0·5 gm. Total dosage 60 mg. per kg. divided into 6 doses (2 daily for 6 days). Children 6–10 one tablet morning and evening first day, same on second, ½ tablet morning and evening on the third. Total 2·5 gm. 10–14 total dosage 3 gm. For adults 1½ tablets first morning followed by 1 tablet the same evening on each of two subsequent days. Total dosage 3·25 gm. For heavy adult (180 lbs.) total dosage 5·5 gm.: 2 tablets morning and evening each of the two first days and on the third morning and one tablet on the third evening. Drug cures 60 per cent. infected with *S. hæmatobium.* Less effective for other types. Overdose produces insomnia and yellow skin discolouration. Miracil D must be kept at high blood level.

Local treatment.—Calculi removed by operation. Perineal cystotomy and drainage. Treat perineal fistulæ, and hyperplasia of cervix and vagina, by scraping.

Prognosis.—Greater exposure to infection means more severe clinical cases. If treated early, prognosis now very good, as calculi and secondary infections are avoided. In mild cases with occasional hæmaturia there is no serious injury to health and usually spontaneous cure. Re-infection must be avoided. At present all natural sources of infection in Africa and Palestine are known.

Prophylaxis (refers also to *S. mansoni*).—Complicated and difficult in heavily infected countries like Egypt. Educational methods (posters, films) necessary. Children especially warned by school and religious teachers against paddling, bathing and washing in rivers, ponds and canals. Clearness of water no criterion. Brackish water safe. Sportsmen shooting duck or snipe should wear gumboots. Drinking boiled water is safe, but chlorinated water is not lethal to cercariæ. Every care must be taken to avoid soiling water supplies by urine or excreta. Measures against molluscs and ova (spawn) ; molluscs widely disseminated by water birds. *Bulinus* soon appears in temporary collections of water in Western Desert, many miles away from Nile. Periodic drying of canals temporarily effective. Canals now treated in Egypt in non-irrigation season—April to July—when they contain less than half normal volume of water, by calculated amount of *sizolin* (creosote derivative), 1 : 20,000, which destroys snails and cercariæ. Difficult to get permanent results owing to opening of sluice gates in spring and restocking of snails from Nile. Organization of antischistosome units in Egypt combines prophylaxis with mass treatment of infected population. Results so far favourable, but necessarily slow. Molluscicides now applied to stagnant canals and drains—Sodium pentachlorate and dinitro-o-cyclohexylphenol (DCHP) at 5 and 10 parts per million respectively.

(2) INTESTINAL SCHISTOSOMIASIS (*Schistosoma mansoni*). (*Bilharzia mansoni*)

Chronic endemic disease with dysenteric and abdominal symptoms and sometimes with splenomegaly. Common in Egypt, Central Africa, Nyasaland.

Geographical distribution and epidemiology.—Probably originally an African disease; imported into W. Indies and S. America by slaves. At present in Africa generally: Egypt, Congo, W. Africa, E. Africa (Abyssinia, Eritrea, Zanzibar, Rhodesia, Tanganyika, Kenya, Madagascar, Natal, Transvaal), S. America, Brazil, Venezuela, Guianas, W. Indies (especially Antigua). In St. Kitts in imported African green monkey (*Cercopithecus sabæus*). In Lake Tanganyika natural infection of house rats found. In Central Africa experimental infection of *Mastomys coucha*, the pouched rat.

Usually more common in men. In Sierra Leone, in adult women. Range of *Schistosoma mansoni* limited by that of intermediate molluscan host, closely associated with *S. hæmatobium*. Areas in S. Egypt, S. Sudan and W. Africa where *S. mansoni* only is found. Infection acquired during period of shallow water, to permit high concentration of cercariæ. In inland lakes, October to January; in backwaters of Nile, February–June.

Ætiology.—*S. mansoni* very similar to, but smaller than *S. hæmatobium*.

Male : 1–1·2 mm. by 1 mm., ventral sucker and wart-like tuberculations more pronounced. *Intestinal canal bifurcates at ventral sucker.* Intestinal cæca unite anteriorly to form single long intestinal tract ; 8–9 small testes.

Female : 1·2–1·6 cm. as in male, intestinal cæca unite in anterior half. Ovary situated in anterior half in front of union of intestinal cæca. Uterus short, usually with few lateral-spined eggs. Shape of bulb of shell-gland determines shape and position of spine.

Habitat.—Inferior and superior mesenteric veins, hæmorrhoidal plexus, portal system. Eggs deposited in subterminal branches of mesenteric veins ; escape aided by lateral spine. In intestine, some pass through muscularis mucosæ *via* capillaries ; when in numbers produce dysenteric symptoms. Eggs : 150 μ by 60 μ, lateral spine, 20 μ ; considerable variation. Miracidium : similar to that of *S. hæmatobium;* may be larger ; if fæces liquid, miracidia escape into lumen of bowel.

Life history:—Development in molluscan host identical with that of *S. hæmatobium;* eggs escape mostly in fæces, small proportion in urine. Development mostly in snail, genus *Planorbis* (*Biomphalaria*)—flat whorled ammon-horned snails like *P. corneus*, common pond snail in England—*Planorbis boiyssi* (Egypt); *P. alexandrinus* and *P. herbeni* (Sudan); *P. neosudanicus* (Nyasaland); *P. pfeifferi* (Sierra Leone, S. Africa, Rhodesia); *P. philippici sub-angulatus* (Tunis); *P. gibbonsi* (Zanzibar); *P. stanleyi* (C.

Kenya); *P. adowensis* (Abyssinia); *P. cultratus* (Venezuela); (*P.*) *Australorbis glabratus* (N. Brazil, Antigua, Venezuela); *A. olivaceus* (Brazil and Dutch Guiana); *A. centimetralis* (Brazil); *A. glabratus*; *A. antiguensis* (Antilles). *Biomphalaria*, new name for *Planorbis*. Races of *S. mansoni* recognized. *Miracidia* from strains of N. African race will not develop in appropriate snails from New World.

Pathology.—*S. mansoni* causes grave changes in viscera. The eggs in numbers in liver cause "pipe-stem" cirrhosis. In mucosa of intestinal canal, the characteristic "sandy patches" are due to effete calcified eggs. Deposition of hæmatin pigment in granules in liver (Kupffer cells). Portal and retroperitoneal lymph glands enlarged. Usually hypertrophy of spleen (Egyptian splenomegaly). Lesions in colon: (1) thickening of mucosa; (2) papillomata; (3) pericolic tumours; (4) polypi, which may extrude from anus, or (in cæcum) cause intussusception. Small intestine rarely affected; sometimes lower ileum. In colon, septic foci and ulceration of bowel caused by tearing off of pedunculated papillomata. Ulcers formed (may be superinfected with *Entamœba histolytica*); sometimes perforation. Small pericolic nodules and lesions in mesenteric glands may resemble tuberculosis. Pulmonary lesions often; embolism by masses of eggs, filtered out by arterioles, producing *arterial* changes resembling Ayerza's disease. In 10 per cent., adult flukes found in pulmonary arteries.

Clinical features.

1. *Stage of invasion.*—Cercarial dermatitis; six weeks later, toxic manifestations as in Katayama disease (*see* p. 204); remittent and intermittent pyrexia, urticaria, abdominal pain, rigors, pulmonary symptoms, cough, hepatic and splenic tenderness; localized deep pain over cæcum. Pronounced leucocytosis (30–50,000) with high eosinophilia (30–76 per cent.).

2. *Stage of deposition.*—Localizing symptoms, diarrhœa, dysentery (blood and mucus with lateral-spined eggs), tenesmus, sometimes choleraic diarrhœa.

3. *Terminal stage.*—Massive abdominal tumours (resembling carcinoma); intestinal stasis and prolapse of hypertrophied papillomata through anus. Infiltration of buttocks with eggs; fistulæ and induration. Cirrhosis of liver with ascites. Pneumonia from deposition of eggs in lungs. Bilharzial appendicitis: massive infiltration of hypertrophied organ. In 50 per cent. in Egypt double infection with *S. hæmatobium* and (almost invariably) with *Ancylostoma duodenale*.

VISCERAL SCHISTOSOMIASIS (Egyptian splenomegaly)

Hepatolienal fibrosis with hepatic cirrhosis and splenomegaly in upper and lower Egypt and in N. Nyasaland; 20 per cent. of children under 4 have splenomegaly with profound anæmia. Formerly thought separate (Banti's) disease. In young, severe course with rickets, in adults cirrhosis with ascites, often complicated by ancylostomiasis.

Spleen very large, perisplenitis. Splenic hyperplasia, not caused by deposit of eggs, but secondary to hepatic cirrhosis. Severe anæmia often of secondary type with advanced blood changes ; eosinophilia not marked ; at first leucocytosis (17,000) with myelocytes, then leucopenia. No intestinal symptoms, sometimes no eggs of *S. mansoni* in fæces, but demonstrable in liver, spleen and other organs by digestion with potash. Some consider it due to infection with "spinster" females, or bachelor males, but this is most unlikely. Irregular pyrexia, vomiting, diarrhœa, œdema, often purpura ; hæmatemesis frequent. Thrombosis of portal vein, sometimes hepatic carcinoma. Venous hum heard by stethoscope over liver. Course of disease may be protracted. Death from hepatic cirrhosis or pulmonary complications.

Pathology.—Spleen average weight : 30–300 oz. (933–9,330 gm.) ; contains a few eggs of *S. mansoni* and shows hyperplasia with macrophage cells. Number of eggs in liver small compared with extensive cirrhosis. Multilobular with isolated necrotic foci. In advanced stages, shrinkage of liver.

Diagnosis.—Lateral-spined eggs in fæces—often scanty ; concentration methods necessary. (Fæces shaken up with dilute HCl, 1 part ; ether, 2 parts ; strained through gauze ; filtrate centrifuged.) When fæces are shaken up with water, eggs hatch and miracidia are easily seen. Sigmoidoscopy, scraping intestinal mucosa and biopsy of papillomata or ulcers. Rectal swab method much used. On rectal examination papillomatous growths may be felt. In 5 per cent. eggs are found in urine. In hepatolienal form increase of euglobulin in serum ; positive formaldehyde test (*see* p. 27)—not reliable in differentiating leishmaniasis. Complement-fixation and intradermal test as in *S. hæmatobium*. Papillomata and granulomata cause localized thickening of colon.

Papillo-adenomata in rectum to be differentiated from piles and carcinoma. Egyptian splenomegaly from kala-azar, Banti's disease, splenic anæmia and other forms of splenomegaly.

Treatment.—Gross changes in organs and deposition of fibrous tissue more extensive than in *S. hæmatobium* infections ; liver especially involved, therefore effects of antimony treatment not so striking. Though adult flukes are killed off, no striking change may be observed in patient. Operative measures may be necessary to remove adeno-papillomata obstructing lumen of colon.

N.B.—*Pentavalent compounds of antimony not effective.*

1. *Tartar emetic.*—In early stages as effective as in *S. hæmatobium*, in same amounts. In Surinam early cases in young adults, given on alternate days : 3 c.c., 5 c.c., 7·5 c.c. of 1 per cent. solution ; total 150–200 c.c. (1½–2 gm.) ; whole course, 6–7 weeks. Some cases require much bigger total dosage, up to 60 gr. (4 gm.). In children in Egypt, rectal injections of 1 per cent. tartar emetic solution daily for 5–7 days are said to be effective.

2. *Fouadin.*—Intramuscularly, as for *S. hæmatobium* (see p. 197) ; not so effective. Several courses required. After 13 injections, signs of drug intolerance appear and may cause death, especially

in double infections with S. *hæmatobium*. If there are renal complications, fouadin is contra-indicated. (Urine gives positive catechol test in fouadin therapy, green with ferric chloride ; violet on adding sodi. bicarb.)

3. *Anthiomaline.*—Intravenously; results better than with tartar emetic (p. 197).
4. *Emetine.*—Efficacious, but toxic. Ten injections, total 9·2 gr. (0·6 gm.). Initial two doses of ½ gr., remaining eight of 1 gr.
5. *Miracil D* has been tried in Egypt, Brazil and elsewhere; not so effective as in S. *hæmatobium* (p. 198).
6. *Operative measures.*—Excision of 12–15 inches of rectal and lower sigmoid mucosa (sleeve operation) ; unsuitable for anæmic or debilitated subjects.
7. *Operative measures for Egyptian splenomegaly.*—Talma-Morrison omentopexy. Splenectomy in early cases successful ; mortality 15 per cent. Ascites, pellagra, cardiac and renal disease are contra-indications. Preliminary treatment with carbon tetrachlorethylene for ancylostomiasis. Neosalvarsan for syphilis. Effects of splenectomy permanent; ascites does not develop.

Prognosis.—As for S. *hæmatobium*. Infections often contracted in clear running water.

(3) EASTERN SCHISTOSOMIASIS

Schistosoma japonicum (*Bilharzia japonica*). Katayama disease (Japan)

Serious chronic endemic disease of Far East. Invasion symptoms severe ; generalized infections common. Infects domestic animals as well as man.

Geographical distribution and epidemiology.—Mostly in Chinese and Japanese, sometimes in Europeans. Local dogs, cats, horses and imported cattle naturally infected. Native cows immune. Infection widespread after floods and inundations. China (Yangtse, in lower reaches), Hunan, Hupeh, Anhwei, Kiangsu and Kiangsi. Near Canton and Foochow. On Burmese border, Yunan, N. Shan States. Japan (Hiroshima and Katayama), S. Formosa, Philippines —Samar, Leyte, Mindanao, Celebes.

Ætiology.—*Schistosoma japonicum* differs in important respects from S. *hæmatobium* and S. *mansoni;* smaller, non-tuberculated, easily transmitted to monkeys, rabbits, mice, rats and guinea-pigs. In Formosa, race of non-human S. *japonicum* in domestic animals, especially pigs.

Male.—9–12 mm. by 0·5 mm. Cuticle and mouth no tuberculations or spines ; 6–8 testes dorsal to ventral sucker. Vasa efferentia form common ducts opening posterior to it in large seminal vesicle. Posterior portion widens, overlapping more extensively than in other species.

Female.—1·2–1·6 cm. by 3 mm. (great variation in size) ; ovary central ; intestinal cæca unite immediately behind it. Well-developed yolk glands extending to posterior extremity. Uterus well developed, wider than other species (containing 50 or more eggs in two rows).

General.—Suckers close together, ventral (acetabulum) funnel-shaped ; suckers and ventral surface covered with small spines, both larger than in *S. hæmatobium.* Œsophagus has *two bulbs*, bifurcation of intestinal canal at level of ventral sucker, but union of cæca more posterior. United gut occupies nearly half body length.

Eggs.—60–80 μ by 40–60 μ, oval, practically spineless, but rudimentary knob-like spine in small depression of shell. In uterus eggs smaller. Extruded from blood vessels directly in intestinal walls, liver, pancreas, mesenteric glands, sometimes brain and spinal cord. Usually in fæces ; sometimes not, but in duodenal juice. Hatch in water ; miracidium has smaller cephalic glands than other species.

Habitat.—Large numbers of worms found at autopsy—as many as 20,000. Inhabits veins of large intestine, gastric, superior mesenteric, splenic, cardiac, pulmonary veins, also *pulmonary artery*; others rarely.

Life-history.—Follows the same lines as preceding species ; losing cilia, miracidium becomes sporocyst in liver and hermaphrodite gland of small, spiral, operculated snail, *Oncomelania* (several species) ; becomes delicate, finger-like sporocyst ; gives rise to 50 or more daughter sporocysts. Cercariæ similar to those of other species—on whole smaller—appear 60 days after infection. Oral sucker especially well developed. Cercariæ phototactic ; cannot survive 50° C. (122° F.) or below 2° C. (35·6° F.), escape into water, penetrate skin. Some minute *Schistosomula* found in liver measuring 150 μ ; attain maturity in 30 days ; eggs in fæces after 35. Reach lungs through pulmonary artery, then travel *via* mesenteric arteries and veins to liver.

Molluscan hosts: Oncomelania (also named *Katayama, Hypsobia, Blanfordia, Hemibia*): *O. nosophora* (Japan and China) ; *O. formosana* (S. Formosa) ; *O. hupensis* (Kiangsu, China) ; *Katayama tangi* (Fukien, China) ; *O.* (*Blanfordia*) *japonica* (Japan, Sadi) ; *O.* (*Hydrobiopsis*) *quadrasi* (Philippines).

Oncomelania.—Small (5–12 mm.), shell long and narrow, multiple whorls. Basal whorl never broader than one above, apex sharp. Mouth of shell ovate dextral ; operculum thin, transparent. Lives in damp places, *not always in water*; buries in earth when climatic conditions unfavourable, continues to harbour cercariæ.

Pathology.—Enlargement of liver and spleen. Liver hypertrophied, nodular cirrhotic ; numerous eggs found on digestion with potash. Spleen fibrous, congested ; eggs scanty ; widespread deposition of hæmatin pigment. Appendices epiploicæ thickened, matted together ; mesenteric and retroperitoneal glands enlarged. Colon and rectum : walls thickened, pericolonic nodules, ulcers and polypi with eggs. Urinary bladder unaffected. Brain sometimes affected : induration of pia mater, and granulomata with eggs in cortex. Schistosomulæ in lungs ; some may reach liver by traversing mediastinum and diaphragm.

Clinical features.—Course usually much graver and more rapid than *S. mansoni*. Massive infections common in some districts, but symptomless cases occur with milder degrees.

Stage of invasion.—Cercarial dermatitis ++, initial fever very severe ("Katayama disease"), urticaria, abdominal pain, paroxysmal cough, dermatographia. Leucocytosis ; eosinophilia 60 per cent. or more.

Stage of deposition.—Great emaciation, dysenteric symptoms, enlargement of liver and spleen.

Terminal stage.—3–5 years, hepato-lienal fibrosis, ascites, œdema of legs, great anæmia, dysenteric symptoms. Jacksonian epilepsy, hemiplegia, blindness (visual centres) ; eggs in brain. Mortality considerable ; death from exhaustion, cholæmia or superadded infections.

Diagnosis.—Urticaria with eosinophilia suggestive. Eggs usually numerous in fæces. Formaldehyde serum test usually +. Complement fixation and intradermal test positive, as in other forms. Biopsy of liver (with liver-puncture ; wide-bore needle), or operation for splenectomy demonstrates eggs.

Splenomegaly to be differentiated from splenic anæmia ; Jacksonian fits from cerebral tumours, cysticercosis, etc.

Treatment.—In early stages : tartar emetic, 24–30 gr. (1·5–1·9 gm.). Most efficacious drug, also cures schistosomæ; Jacksonian epilepsy in Europeans. Fouadin in similar doses (see p. 197) widely employed in China, but most cases are in terminal stages before seeking treatment. Splenectomy not usually successful on account of advanced cirrhosis of liver. Emetine also used (see p. 197), but verminous thrombosis of portal vein may ensue. Miracil D useless.

Prophylaxis.—Drying up ditches is no good, *Oncomelania* being operculated. Lime (1 per cent. solution) used. Application of steam jet to mud to destroy snails. 1 : 200,000 copper sulphate solution used whenever possible. Rubber waders to be worn by sportsmen. Education much less valuable, as domestic animals, especially dogs, infected. Snail vectors live in inaccessible places. Sodium pentachlorophenate (santobrite) applied to soil, 390 mg. per sq. foot, twice yearly to ditches, banks and rodent burrows. At this concentration harmless to man and domestic animals. Results encouraging. 10 pts. per million cyclohexyl-dinitrophenil said to be better.

OTHER TREMATODES

Gastrodiscoides hominis

Geographical distribution.—Malaya, Assam, India, Burma, Cochin-China, British Guiana. Normal host : pig, mouse-deer.

Ætiology.—*G. hominis* reddish from hæmoglobin. When alive, expansive—elongates to 1 cm. and shrinks to 5–7 mm. by 3–4 mm. Anterior sucker conical; posterior discoidal, flattened ventrally to concave disc; prominent genital papilla 2·5 mm. from oral sucker. Ventral sucker large (2 mm. in diameter). Cuticle smooth. Pharynx with two pear-shaped pharyngeal pouches; two lobulated testes; ovary in midline posterior to testes. *Eggs:* 152 μ by 60 μ, operculated. Life history unknown.

Habitat.—In cæcum in large numbers; induces no symptoms; eggs in fæces.

Treatment.—Thymol and tetrachlorethylene effective.

Pseudodiscus (*Watsonius*) *watsoni* once found in negro in S.W. Africa. Normal host, monkeys: *Cercopithecus* and *Papio*.

CHAPTER XIV

METAZOAL DISEASES: NEMATODE INFECTIONS

ASCARIASIS

Infection of alimentary tract, mostly small intestine, of gorilla and large apes and man, with roundworm, *Ascaris lumbricoides*. *A. suis* in pig indistinguishable.

GEOGRAPHICAL DISTRIBUTION AND EPIDEMIOLOGY

World-wide, especially in tropics, in China, India and Pacific Islands. A disease of insanitation.

ÆTIOLOGY

A. lumbricoides.—Large, like earthworm. Round, tapering at both ends. Mouth anterior, guarded by thin lips with finely denticulated margins; anus subterminal.

Female.—20–35 cm. by 3–6 mm.; paired genital tubes, containing uterus, receptaculum seminis, oviduct and ovary; tubes and ducts attain length of 125 cm. Total capacity 27 million eggs; average daily output 200,000; 2,400 eggs by one female for each gm. of fæces.

Male.—15–31 cm. by 2–4 mm.; yellow or brown, with white longitudinal lines; tail curved in semicircle; two rows of tactile papillæ and two chitinous spicules.

Egg.—50–70 μ by 40–50 μ, elliptical, encased in albuminous coat with mamillated appearance; stained brown by fæcal pigments.

Life history.—Eggs in fæces ; no segmentation or differentiated embryo. Live in water or moist earth, requiring warmth (36–40° C.) (96·8–104° F.) for 2–4 months. Embryo, coiled and moving inside egg-shell, hatches in small intestine on being swallowed. Shell softened by gastric juice. Larvæ penetrate mucous membrane, enter blood, *via* heart and lungs, in alveoli (" blood bath ") 10–14 days. Thence into trachea ; swallowed ; reach intestine. Larvæ 1·3–2 mm. on 10th day, 1·75–2·37 mm. on 15th.

PATHOLOGY

Larvæ damage lungs : hæmorrhage, toxic absorption, eosinophiles in alveoli. In lungs grow ten times larger and while migrating feed on blood, causing considerable damage and pneumonia. Aberrant migrations to thyroid, thymus, spleen ; rarely to brain and spinal cord. Sometimes general peritonitis by perforation of intestine as in liver abscess.

CLINICAL FEATURES

Larvæ.—In hyper-infection respiratory symptoms appear from 26 hours to 4–5 days after ingestion of eggs. Clinical picture of lobar pneumonia in children. *Adult worms.*—Usually abdominal pain (colic), urticaria and protuberant abdomen, but in many no obvious disturbance. Nausea, capricious appetite, dark rings under eyes. Large masses cause intestinal obstruction and intussusception. In stomach produce vomiting; in rima glottidis, asphyxiation. Enter bile-ducts and cause abscess of liver, especially in Singapore: pearl-like nodules with eggs in peritoneum and mesentery. Enter lumen of appendix and cause appendicitis. In women sometimes become encysted in Fallopian tubes.

Toxin : *ascaron* (albumoses and peptones) may cause anaphylaxis, shown by conjunctivitis, asthma, urticaria and fever.

DIAGNOSIS

Eggs in fæces ; concentration methods usually necessary. " Couillard's sign " : redness of fungiform papillæ on tongue. X-rays : barium meal displays ascaris as cylindrical, coiled filling defect with string-like shadow caused by barium inside parasite, especially in small intestine. Usually eosinophilia, especially in invasion stage ; not very reliable. Eosinophilia 9·9 per cent. in European children, 5·3 per cent. in negroes. Intradermal and scratch tests of little value.

TREATMENT

Oil of chenopodium more effective in capsules (min. 3 (0·186 c.c.) each) ; maximum adult dose, 24 min. (1·421 c.c.), in two equal portions; probably better with tetrachlorethylene (see p. 211), preceded by ½ oz. (15·5 gm.) of sodii. sulph. the night before and again ½–1 hour after.

N.B.—Dead worms may not be passed for 7 days after treatment.

Atebrin (mepacrine) in full dose 0·9 gm. at night followed by a saline aperient next morning kills ascaris and stains them yellow.

Piperazine—Piperazine citrate (*Antepar*). For adults 3 gm; for children 2 gm. followed by aperient very effective. Piperazine adipate (*Entacyl*) tablets of 300 mg., 2 three times daily for three days.

Hetrazan—" Nilodin " (diethyl carbamazine), 10 mg. per kg., in three equal doses after meals for 3 days; interval of 1½ hours after food should elapse, otherwise nausea and vomiting. More than one course necessary. Some are intolerant.

Physaloptera caucasica.—(*P. mordens*) resembles small Ascaris. Normal host : monkeys. In man in Central Africa, Portuguese E. Africa, Uganda, Nyasaland. In œsophagus, stomach, small intestine ; occasionally liver.

Female.—24 mm.–1 cm. by 1·14–2·8 mm. ; posterior end tapers to sharp point : two ovaries ; single uterine tube.

Male.—14–50 mm. by 0·7–1 mm. ; tail has two lateral cuticular alæ ; numerous papillæ ; two spicules of unequal length.

Both sexes.—Mouth guarded by two large lips, armed with two papillæ, and rows of teeth.

Egg.—45 μ by 35 μ, double contour, thick, colourless, smooth shell.

Life history.—Unknown—insects possibly. Clinical symptoms indefinite.

Lagochilascaris minor, normally parasite in intestine of cloudy leopard cat, *Felis nebulosa*; reported mostly in mastoid abscesses. Recently found commonly in Surinam in large numbers in subcutaneous abscesses.

Female.—15 mm. by 0·5 mm. The uteris and ovaries in middle third.

Male.—9 mm. by 0·4 mm.

Both have triangular cuticular ledge along lateral line. Three large lips covered by cuticle, each with vertical cleft. Labial structure separated from body by annular furrow.

ANCYLOSTOMIASIS (Hookworm Disease)

A chronic disease characterized by great anæmia, debility and cardiac failure, due to absorption of toxins of *Ancylostoma duodenale* and allied form *Necator americanus* inhabiting small intestine, often in great numbers.

Ancylostoma duodenale.—" Old World Hookworm."—Both sexes cylindrical, white-grey or reddish (ingested blood).

Geographical distribution and epidemiology.—Widespread in tropical and subtropical countries, especially Egypt, Siam, S. China, Malaya, India, Ceylon, E. Indies, most Pacific Islands, N. and S. Queensland, W. Indies, South U.S.A. and S. America. Has been found in Belgium, Germany, Italy and in tin mines of Cornwall. Occurs wherever sufficient warmth and gross insanitation ; bare feet, absence of efficient latrines. Requires temperature of 75° F. (24° C.) for development outside body.

Ætiology

Female.—10–13 mm. by 0·6 mm. ; slightly expanded posteriorly ; vagina in posterior third. Body cavity contains ovary and coiled uterine tube with eggs. Maximum egg output 15–18 months after infection.

Male.—8–11 mm. by 0·4–0·5 mm., copulatory bursa at posterior end ; umbrella-like expansion ; dorsal ray branches distally into small bifurcating rays ; two long, delicate spicules—genital papillæ. (Owing to situation of genital openings in both sexes worms in copula assume Y-shaped figure.)

General features.—Two anterior cephalic glands secrete anticoagulating ferment. Mouth bent dorsally ; buccal capsule, lined with chitin, contains two pairs of sharp teeth in ventral aspect of buccal cavity.

Habitat.—Mostly jejunum, to a lesser extent duodenum ; not ileum. Numbers at autopsy great : 500–1,000. Life span : 4–7 years. Egg-laying capacity of female : 30 eggs per c.c. fæces *per diem*. Egg-count falls as worm-count increases.

Egg.—60 μ by 40 μ, elliptical, transparent shell ; when freshly laid, contains 2–4 blastomeres.

Necator americanus.—" New World Hookworm."—Resembles and produces same effect as *A. duodenale*, similar life history. Shorter and slenderer.

Geographical distribution.—Not only America, common in W. Africa, Ceylon, Pacific Islands, Malaya, Philippines ; amongst aborigines of Congo and Central Africa ; 90 per cent. of ancylostomes in tropics are of this species. Also in gorilla, Patas monkey, rhinoceros.

Female.—8–11 mm. by 0·4 mm.

Male.—7–9 mm. by 0·3 mm. ; copulatory bursa closed and blunt ; short dorso-median lobe appears divided ; dorsal ray branches at base into divergent arms with bipartite tips ; two separate spicules unite to form single terminal " fish-hook " barb.

General features.—Sudden dorsal bend of head (esp. in female) distinctive. Buccal capsule smaller than in *A. duodenale;* irregular border ; in place of 4 hook-like teeth, ventral pair of *cutting plates;* outlet of dorsal gland (" dorsal rib ") projects into oral cavity ; deeply placed in capsule are one pair of dorsal and one pair of submedian lancets.

Egg.—64–75 μ by 36–40 μ, on average, smaller than *A. duodenale.*

Ancylostoma braziliense.—In dogs and cats in Brazil ; civet cat in Ceylon ; found rarely in mixed hookworm infections in India, Malaya, Siam. Smaller than *A. duodenale.* Internal pair of ventral teeth smaller than those of *A. duodenale.*

LIFE-HISTORY OF HOOKWORMS

(1) *Egg* deposited in lumen of intestine ; 2, 4, 8, blastomeres.

(2) *Embryo* moves inside shell in fæces and soil ; gives rise to

(3) *Rhabditiform larva* which burrows into fæces, feeds on bacteria. At first has double œsophagus ; food reserves (oil globules in intestinal wall). Two moults ; œsophageal bulb disappears ; larva then leaves fæces, enters earth, and becomes

(4) *Infective filariform* (third stage) *larva:* well-developed mouth capsule ; simple muscular œsophagus. Moves towards oxygen supply. Protected by sheath to withstand desiccation ; can live in damp soil (in optimal conditions) for 2 years ; encysts on blades of grass and may enter droplets of dew and in this manner entrance to skin is facilitated.

(5) Penetrates ***human skin;*** sheath discarded ; enters lymphatics ; gains blood-stream ; reaches lungs on third day. Then breaks through alveoli ; enters bronchioles and travels *via* trachea and œsophagus to stomach. During migration has third moult and " terminal buccal capsule " is formed. In intestine on 7th day has 4th moult ; " terminal buccal capsule " changed into " provisional buccal capsule " ; mouth opening directed dorsally as in adult, without teeth. On 15th day " provisional buccal capsule " is cast ; takes on adult form with adult buccal capsule and bursa of male. In 3–5 weeks is sexually mature. Ancylostome larvæ can be " cultivated " in Petri dish with warm water and blotting paper, forming uniform layer like peasoup.

PATHOLOGY

Fifty-three per cent. classified as " hookworm disease " ; remainder as " carriers of worms." Anæmia due to chronic loss of blood ; absorption of toxins ; bacterial infection of damaged small intestine. Generalized œdema ; fat increased. Effusions into serous cavities. Heart, liver and kidneys dilated, flabby, fatty. Ancylostomes in numbers in duodenum and jejunum ; attached to bowel or in mucus. Numerous small blood extravasations ; blood cavities in submucosa ; occasionally clots of blood in lumen. Bone marrow hyperplastic, dominant erythropöiesis. Microscopically : toxic degeneration of parenchyma cells of liver ; hæmosiderin granules + ; also free iron (Prussian blue reaction).

Clinical pathology.—Blood picture typical of iron-deficient hypochromic microcytic anæmia. Red cells may be as low as one million; average 1,400,000. Hæmoglobin may be as low as 10 per cent. ; percentage content of hæmoglobin does not correspond to actual deficiency, owing to increase of blood volume. Colour index usually 0·7 ; may be as low as 0·5 ; mean corpuscular volume below normal ; occasional normoblasts ; reticulocyte count less than 3 per cent. Van den Bergh reaction negative ; decrease in plasma protein and plasma albumin with increase of globulin. Œdema due to reduction of colloid osmotic pressure. Abstraction of blood by ancylostomes is important feature ; as is also secretion of anti-coagulant ferment. Gastric juice usually shows achlorhydria and hypochlorhydria.

CLINICAL FEATURES

Stage of invasion.—Ancylostome dermatitis ("ground itch," "water itch") due to penetration of larvæ, occurs 2–4 months before generalized symptoms, in rainy season; dermatitis of feet, vesiculation and pustulation. (Some species—*A. braziliense*—may cause "larva migrans"). Inboring of larva guided by *thermotaxis*, facilitates entrance of bacteria. Prevention consists in wearing foot-covering in wet season; useful to immerse feet in tar; labourers on irrigated land should wear well-fitting boots and take antiseptic foot baths of 3 per cent. salicylic acid in ethyl alcohol.

Stage of deposition.—Dietetic factor important; lack of proteins decisive in determining deposition. Daily loss of blood; anæmia usually marked—"earthy colour." Dyspepsia and gastric distention common; epigastric tenderness—"duodenal pain" closely simulated; abnormal appetite; perverted taste—*pica, geophagy*. Melæna sometimes; stools always contain "occult blood," sometimes blood-stained mucus. Continued fever frequent. Skin pallid; face puffy; œdema of feet and ankles. Lassitude, palpitations, breathlessness, dimness of vision. Hæmic murmurs over base of heart and larger blood vessels. Retinal hæmorrhages.

Terminal stages.—Increasing anæmia, œdema, terminal diarrhœa with passage of mucus and sometimes blood. Death from cardiac failure, melæna, anæmia.

Psychological effects.—Social factor important. Ancylostomiasis produces deterioration in race and characteristics; prolonged exposure produces "poor mean white," "beach-comber." Children stunted physically and mentally; sexual development delayed; emaciated, with "pot-belly"; "germ of laziness"; indolent, untrustworthy, predisposed to crime.

In pregnancy.—Repeated abortions and miscarriage. Heavy maternal and infantile mortality. Predisposes to toxæmia—eclampsia and toxic nephrosis. Decompensated impairment of renal function during gestation.

Surgical operations.—Deleterious factor in major surgical operations in tropics; treatment for hookworm essential before operation. Ancylostomiasis patients take anæsthetics badly.

DIAGNOSIS

Demonstration of ancylostome eggs in fæces; concentration methods usually necessary in Europeans (anything below 70 eggs per gm. of fæces cannot be found by direct microscopic method). Direct centrifugal flotation: eggs float up in concentrated salt solution. Fæces disintegrated by vigorous shaking in water in closed tube, centrifuged for 1 minute at 1,000 revolutions. Supernatant fluid decanted, solution of salt of specific gravity of 1,150 added, centrifuge again for 30 seconds at 1,000 revolutions; tube filled so that saline lies in contact with under-surface of cover clip. Eggs adhere to under-surface of glass and can be removed and examined by hanging-drop preparation.

Simple flotation method dispenses with centrifuge : 2 gm. fæces rubbed up in saturated salt solution in wide tube filled to brim, slide or cover glass in contact with fluid 10 min. ; eggs adhere to glass.

Subsidiary measures.—Positive occult blood test in fæces. Charcot-Leyden crystals. Eosinophilia in blood usual ; high in invasion stage ; may be 60 per cent. ; falls during progress of disease ; terminal stages : no eosinophilia. Diagnosis by vermifuge (tetrachlorethylene) and recovery of worm in fæces, in U.S.A.

TREATMENT

On account of debility, anæmia and cardiac state, care must be exercised in administration of anthelmintics.

1. **Oil of chenopodium**—" wormseed " (active principle : *ascaridole*) given in gelatin capsules on account of sharp, burning taste ; rapid absorption, in toxic doses causes depression of respiratory centres. Maximum dosage: 3 c.c. (51 min.); usually in capsules of 3 min. (0·185 c.c.) each. For children, 1 min. (0·062 c.c.) each year up to 16. Give 3 *hours after light meal*; and ¼–½ hour later give saline purge (sodi. sulph. ½ oz. : 15·5 gm.) to expel worms. Ol. ric. preferred by some, but may increase toxicity. Contra-indicated in nephritis, cardiac disease, hepatic dysfunction and intestinal ulceration.

2. **Carbon tetrachloride (tetraform)** and **tetrachlorethylene** (which is less toxic and has largely superseded the former) are used for mass treatment ; absorbed from stomach and intestine, passed out in fæces combined with fat and fatty acids. Absorption produces dizziness and drowsiness ; rarely may give rise to delayed toxic jaundice. Acute carbon tetrachloride poisoning imitates acute abdomen and may simulate yellow fever. Treatment not to be repeated ; apt to produce hepatic cirrhosis. Alcohol and absorbable fat contra-indicated during treatment. Adult dosage : 1 dr. (3·6 c.c.) in hard gelatin capsules in two capsules 30 min. (1·86 c.c.) each after fast of eighteen hours. No preliminary purgation. Sodii. sulph. ½ oz. (15·5 gm.) given 15–30 minutes afterwards, and hot water enema. Dead ancylostomes not passed in first stool ; may continue to appear for 3 days subsequently.

3. **Combined (synergic) treatment.** Efficacious. Tetrachlorethylene and oil of chenopodium in gelatin capsules after partial starvation for 12 hours.

    8.30 a.m. 2 capsules of oil of chenopodium, 7½ min. (0·45 c.c.) each.
    8.45 a.m. Tetrachlorethylene, 40 min. : 4 capsules of 10 min. (0·6 c.c.) each.
    9. 0 a.m. Mag. sulph. (or sodii. sulp.) 1 oz. (31·1 gm.) in water.

    Stools become liquid in 4 hours ; if not, repeat mag. sulph.

N.B.—Eggs are passed for days (up to 6) in stools after effective treatment. If eggs persist, course must be repeated, but at least 7 days must elapse.

Or in mixture :	Tetrachlorethylene ..	min. 40 (2·48 c.c.)
	oil of chenopodium ..	min. 17 (1 c.c.)
	liquid paraffin ..	1 oz. (29·5 c.c.)

in two doses of ½ oz. each followed by saline purge.

Hexylresorcinol much used in U.S.A. ; non-toxic ; pills or gelatin capsules, 3 gr. (0·2 gm.) each. Must be swallowed whole: if chewed excoriates mouth.

For adults and children over 12	5 pills.
8–12	4 ,,
6–8	3 ,,
under 6	2 ,,

No food for 4 hours after treatment. Alcohol contra-indicated. Saline purge 1 day later.

After treatment.—Prolonged dosage with iron (ferrous sulphate tablets) necessary ; occasionally blood transfusions.

Prophylaxis.—Contamination of soil is main factor. Tea, coffee cocoa, banana, mulberry, citrus fruit and rubber plantations are serious sources and supply many carriers in small area. If inhabitants defæcate under trees, the conditions necessary for development are provided in the accumulation of fæces ; warmth, moisture (dew better than rain) and shade ; infective larvæ are killed in a few minutes by sunlight. *Latrine* provision very important ; shallow trench covered with soil provides good conditions (larvæ migrate vertically—rarely laterally). Heavy rain washes away fæces and is a good preventative (larvæ cannot live in water). Rise in temperature increases activity. If food reserves of larvæ are used up, in tropics, rarely survive more than 6–8 weeks. By the Chinese system of night-soil preservation larvæ are killed. Water supply guarded and drinking water boiled. No raw fruit or vegetables should be eaten from garden fertilized by human fæces. Soil should be treated to exterminate larvæ (larvæ demonstrated by Baerman method : soil placed in funnel closed by rubber tube and clip with 1 mm. mesh brass sieve ; level of water 2·5 cm. above bottom of sieve. Lined with cotton fabric ; on standing, larvæ collect in rubber tube.) Education in schools by diagrams and instructional films plays important part in health propaganda.

Intensive mass treatment, with oil of chenopodium and tetrachlorethylene, is no use unless satisfactory latrines were established one year previously. " Bore hole " latrine, 16 in. diameter, carries risk of infecting subsoil with pathogenic bacteria ; it is, however, a method acceptable to natives, and abolishes odour and flies. Education of children important. Cinema films have been successful in inducing people to be examined and treated.

ŒSOPHAGOSTOMIASIS

Œsophagostomum apiostomum, encysted under mucous membrane of large intestine, produces condition like polyposis: common parasite of cæcum and colon of monkeys in Africa, Philippines and China. In man in N. Nigeria.

Ovoid expansion of cuticle at anterior end, limited by oral ring.

Female.—10 mm. by 0·325 mm., posterior, terminating in sharp point; vulva in anterior half.

Male.—8–10 mm. by 0·35 mm.; copulatory bursa with dorsal ray bifurcating into branches; horse-shoe shaped structure.

Egg.—60 μ by 40 μ, closely resembles ancylostome in advanced stage of development.

Life history.—Larva hatches from eggs in soil as unsheathed rhabditiform; this is swallowed, passes through stomach and intestines and invades wall of cæcum where it forms nodules; breaking out into lumen, attached to mucosa, becomes adult.

Clinical features.—Dysenteric symptoms.

Treatment.—Phenothiazine effective: in small doses 0·5 gms. for three days.

O. stephanostomum closely resembles above: found in man in Brazil with dysenteric symptoms.

OTHER INTESTINAL NEMATODES OF LESS IMPORTANCE

Gnathostoma spinigerum, or *siamense*, parasite in stomach of tiger, dog and cat in India, Malaya, China, Japan. Reported in advanced larval stage in man in Siam. From consuming uncooked preserved fish which contains encapsulated third-stage larvæ. Eggs of adult worms have been found in human fæces.

Female—25–54 mm.

Male.—11–25 mm.

Reddish in colour. Globular cephalic swelling separated by cervical constriction. Anterior half provided with leaf-like spines.

Ternidens deminutus.—In man, in Nyasaland, Portuguese E. Africa, and Transvaal ; also in monkeys and baboons in Africa and Asia. Not pathological unless in large numbers in cæcum.

Female.—14–16 mm. by 0·73 mm. ; genital orifice posterior and subterminal ; short vagina opens into two uterine tubes.

Male.—9·5 mm. by 0·56 mm. ; copulatory bursa ; dorsal ray divides into two distal extremities ; each branch formed again and bifurcates.

General characters.—In appearance resembles ancylostomes ; anterior extremity not bent ; mouth capsule terminal, with corona of setæ ; three serrated teeth guard entrance to œsophagus.

Egg.—84 μ by 40 μ, delicate, transparent, resembles ancylostome in advanced segmentation.

Life history.—Rhabditiform larva, 0·3 mm., with flagellar tail, hatches from egg in soil : becomes sheathed and infective filariform larva (0·6–0·7 mm.). Can survive desiccation, reviving in water.

Trichostrongylus colubriformis.—Normally parasitic in upper small intestine of sheep and goat ; duodenum and upper jejunum of man ; in agricultural districts of India, Persia, C. Africa, Egypt, Japan and Korea. Probably quite common. Eggs not infrequent in ancylostomiasis cases in India and Assam.

Female.—4–6·5 mm., outnumbers male, slender, pink, anterior extremity contains attentuated vulva in posterior quarter.

Male.—4·5 mm. by 0·07 mm ; bilobed copulatory bursa ; two spicules.

General characteristics.—Found in mucus covering mucosa near duodenum. Scraped on slide, worms appear as red streaks ; seen against dark background on slide shaken in saline in Petri dish. Mouth unarmed.

Egg.—63 μ by 41 μ, relatively large ; oval, thin-shelled, contains morula when deposited. Likely to be mistaken for ancylostome ; translucent, smaller.

Life history.—Eggs hatch outside body ; rhabditiform larvæ metamorphose into infective filariform in 6 days at 22–25° C. Enter body by skin or mouth. Same course as ancylostome. Eastern form in Japan separated as *T. orientalis* or *T. probolurus*. Also natural infection of gazelle and camel ; but rare in man. Usually no symptoms, may cause secondary anæmia. Worms easily expelled by tetrachlorethylene, 1 dr. (3·75 c.c.).

Strongyloides stercoralis.—Larval form frequently found in fæces; pathogenicity doubtful ; confused with other nematodes, principally ancylostomes. Can produce condition like *larva migrans.*

Geographical distribution.—Almost world-wide, especially in tropics : Brazil, Cochin China. In man only.

Clinical.—No symptoms usually—diarrhœa described also condition affecting buttocks and loins, resembling *larva migrans*, possibly due to migration of larvæ in the skin. In infected persons allergic urticarial eruptions due to toxins of larvæ of strongyloides. Pulmonary changes also described, producing bronchopneumonia.

Ætiology.—Adult forms parasitic in submucosa of small intestine ; considered to be parthenogenetic females, but now claimed that parasitic male exists—shorter and broader than female, resembling free-living form. *Real sexual cycle* carried out in fæces outside body.

Female: (in intestine), 2·5 mm. by 0·034 mm., tapering anteriorly ; conical tail. Mouth with three lips leads to œsophagus occupying quarter of body. Vulva in posterior third. Prominent uterus contains 50 eggs. Rhabditiform larvæ, produced in 3–4 days, develop into filariform infective stage and re-enter definitive host *via* skin or buccal mucosa.

Parasitic Male: tail curved ventrally—two spicules and gubernaculum.

Egg: 50–58 μ by 30–34 μ, deposited in lumen of bowel in advanced stage of development, hatches immediately into embryos, 0·2–0·3 mm. by 0·013 mm. ; double-bulb œsophagus. Passed active in fæces; free-living, develop in 3–5 days into free-living non-parasitic male and female forms, with rhabditiform double-bulb œsophagus.

This male is 0·7 mm. by 0·035 mm. and the female 1 mm. by 0·05 mm. Copulation takes place in the fæces. The rhabditiform larvæ are indistinguishable from those derived from parasitic female. After 3–4 days, develop into post-feeding mature filariform larvæ which are the infective stage and re-enter human host *via* the skin or buccal mucosa, but remain alive in soil for many weeks. Distinguishing feature from larvæ of *Ancylostoma* and *Necator* is œsophagus which is half the length of the body, but in the latter it occupies a quarter.

SCHEMATIC SUMMARY.

Intestine.	Female, parasitic intestinal (Parasitic male ?) produces Eggs hatching in intestine
Fæces.	produce rhabditiform larvæ which develop into (*a*) infective or (*b*) sexual forms which copulate and females lay :
Fæces.	Eggs from which emerge second rhabditiform larvæ—moult and become filariform—enter man by penetrating skin or through mouth. *Migrate through lungs to œsophagus* in manner similar of that of ancylostome. In two weeks develop into parasitic females in small intestine.

Diagnosis.—Easy by active larvæ in *fæces*. Duodenal intubation more certain method. Often found in diarrhœa, especially sprue.

In large numbers probably cause irritation of bowel and diarrhœa, abdominal pain, flatulence, usually in men. At autopsy found in large numbers coiled in intestinal follicles.

In infected patients there is supersensitization to antigens of parasite, and urticaria at site of entrance of parasite, or on rubbing extracts into skin (Fülleborn). Often causes periodic urticarial eruptions in vicinity of anus and often on trunk and thighs. Sometimes petechial, rarely linear, like *Larva migrans*. Possibly due to penetration of skin by larvæ. During pulmonary migration larvæ produce bronchopneumonia.

Treatment.—Thioxanthone (*Miracid D or Nilodin*) specific oral dosage 5–20 mg. per kg. in divided doses for 6 days. Short cure is 20 mg. per kg. for 2 days.

S. fülleborni, parasite of monkeys, has been recovered from American soldiers in S.W. Pacific.

OXYURIASIS. THREAD OR PINWORM

Oxyuris vermicularis (*Enterobius vermicularis*).—World-wide (45 per cent. of schoolchildren infected ; very common in adults in tropics).

Habitat.—Lives in upper portion of large intestine, especially cæcum and appendix, occasionally vagina, rarely ear and nose.

Small, white, thread-like ; mouth surrounded by cuticular expansion (halo) ; skin transversely striated ; the only nematode in man with double-bulb œsophagus in adult.

Male.—Seldom seen, 2·5 mm., much smaller and does not migrate like female. Posterior third curved spirally ; caudal extremity blunt ; six sensory papillæ ; single spicule, 70 μ.

Female.—9–12 mm. ; long, pointed tail ; anus 2 mm. from posterior extremity.

Egg.—50–54 μ by 20–27 μ, flattened on one side, colourless, double-contour, shell bean-shaped ; contains almost fully-formed embryo.

Life history.—No multiplication of worms in body. Fertilized female migrates out of anus, deposits eggs in natal folds. After a few hours embryo develops and grows to 140–150 μ. Taken into mouth, generally under finger nails, it hatches in digestive juices. Larvæ pass, after two moults, from small into large intestine, where they become mature. Duration of cycle, two weeks.

Retrofection described by Schüffner in which infective larvæ re-enter the anus.

DIAGNOSIS

Cellophane " N.I.H." swab makes it possible to scrape eggs from perineum and recognize them under microscope. Females may be seen outside anus at night. Occasionally eggs found in fæces. Does not cause eosinophilia. Number infecting host determined by number of eggs swallowed. Scotch tape method by which ova adhere to surface found useful and simple.

CLINICAL FEATURES

Mature worms penetrate mucosa, encyst in submucosa of large intestine or appendix, and cause appendicitis in 2 per cent. ; found in lumen. Nasal itching common ; also pruritus ani. Familial infections common.

TREATMENT

In adults may be difficult. For *pruritus:* ung. hydrarg. ammon. to anus. Raw carrot diet, cut down sugars and carbohydrates. Great many remedies.

Hexylresorcinol.—In U.S.A., by enema, 1 : 2,000 solution, after soap and water enema : 2 pints to adult and to limit of tolerance in children. One every 3 weeks. No better results when taken by mouth.

Piperazines.—Recent discovery in Antepar (piperazine hydrate, in syrup (150–70 mg. per kg. per day) and Entacyl (piperazine adipate) with mild aperient—syrup of figs or senna (see p. 247).

Threadworms often disappear after a barium meal. The barium finds its way into every crevice of the intestine. *Barium sulphate* in 75 per cent. concentration in six ounce meal of umbrose; a second dose is taken 3 hours later and followed by calomel. The process is repeated next day. The dose for children is three-quarters that for adults.

Prophylaxis.—General measures. Sleeping in cotton drawers, cotton gloves, paring finger nails, and washing hands after defæcation.

TRICHURIASIS. "WHIPWORM"

Trichuris trichiura (*Trichocephalus dispar*).—Distribution: world-wide; more in tropics than elsewhere; in many countries 50 per cent. of population infected. Produces no special symptoms. Identical with species in pig.

Male.—30–45 mm., attenuated portion contains cellular œsophagus; half as long again as thicker posterior portion. Caudal extremity curved ventrally. Single spicule in sheath studded with spines.

Female.—30–50 mm., anterior attenuated portion twice as long as posterior, which is occupied by stout uterus and eggs. Females preponderate to male, 466 : 1.

Egg.—50 μ by 22 μ, characteristic barrel shape, brown, single shell with plug at each end, unsegmented embryo.

General characteristics.—Greyish-white or pink. Lives in cæcum; maintains position by transfixing fold of mucous membrane by slender neck.

Life history.—Spread by stale fæces. Eggs unsegmented; embryo develops slowly, attaining full length in 6–12 months. Can withstand low temperature owing to thick shell and lie latent for 5 years. Development direct. Embryo hatches when egg is swallowed; egg-shell digested by intestinal juices. Larva passes to cæcum or colon, adheres to mucosa, becomes adult.

CLINICAL FEATURES

No special pathology. Some claim it causes diarrhœa. Has been seen in mucosa by sigmoidoscopy; in rectum, may cause rectal prolapse in children.

TREATMENT

Difficult to expel. Worms may be very numerous. Recent report of over 1,000 removed.

Piperazines.—Recently found effective, such as :—

Entacyl (Piperazine adepate). The hydrate salt not recommended.
Two tablets (300 mg.) three times daily. Up to 6 years 1 tablet for each year of life for week or ten days. In syrup form more suitable for children.

Hexylresorcinol 1 : 2,000 solution advocated. Bowels first cleansed by soap and water enema and 2 pints of former for adult, less for children, injected one enema weekly for three.
Warm hydrogen peroxide solution (1·5 per cent.) gradually introduced into intestine removes these worms.

Capillaria hepatica (*Trichocephalus hepaticus*).—Closely allied to *T. trichiura*, normally parasite of liver of rat, where eggs are deposited in masses. Life cycle like *T. trichiura*.

In British soldiers in India. Septic pneumonia secondary to abscess of liver caused by adult worms. Eggs in liver substance, not in fæces.

TRICHINIASIS

Trichinella spiralis.—White worm just visible to eye.

Distribution.—World-wide. Formerly common in Germany and France ; now in U.S.A., China, Syria, India (from eating wild pigs), Algeria, E. Africa. Rare in Australia. Outbreaks in England and S. Wales from eating sausages. Pigs, wild boar, bears, rats, commonly infected. Laboratory animals, including lizards, capable of infection. Birds refractory. Infection normally from pig to rat, rat to rat (sick rats eaten carnivorously). Man not normal intermediary.

Male.—1–6 mm. by 0·04 mm., cloaca posteriorly between two caudal appendages ; two pairs of papillæ.

Female.—3–4 mm. by 0·06 mm. ; vagina in anterior fifth ; ovary in posterior half ; anterior occupied by coiled uterine tube ; anus terminal.

Egg.—20 μ in upper uterus ; embryo soon breaks loose and lives free in uterine cavity.

Viviparous embryos voided into lumen of intestine, 100 μ by 6 μ.

Habitat.—Small intestine ; embryos emitted by female migrate into muscles, where they encyst. Cysts very small ; cannot be seen by meat inspection unless by microscopic examination or when calcified. Male dies after copulation: female 5–6 weeks after discharging hundreds of embryos.

Life history.—Embryos travel by lymphatics and veins ; pierce coats of vessels ; encyst in striated muscles—diaphragm, intercostals, laryngeal and tendinous insertions.

CLINICAL FEATURES

Stage of invasion.—Symptoms resemble cholera and dysentery with hyperpyrexia (T. 104–106° F.). During migration of larvæ through tissues, typhoidal symptoms with remittent T., muttering delirium, muscular pain, leucocytosis and high eosinophilia.

Stage of deposition.—Encystment in muscles in 3 weeks : profound cachexia, toxic absorption ; œdema of face, abdomen and legs ; pruritus, skin eruptions. Blood and albumin in urine occasionally.

Terminal stage.—Death usually in second stage. Recovery : fever resolves but muscular pains persist. Moderate eosinophilia.

DIAGNOSIS

Eosinophilia very high in acute stage ; may be 60–90 per cent. ; decreases in chronic ; absent after 9 years. Adult worms and embryos in fæces. In chronic rheumatoid stage, cysts identified under microscope by biopsy ; when calcified, by X-rays. At autopsy found in pectoral, diaphragm, laryngeal muscles ; best method : digestion of 50 gm. muscle by artificial gastric juice. In living subject small portion taken by biopsy can be treated similarly.

Subclinical trichiniasis in 1 per cent. of population of Great Britain.
Precipitin test with extract of parasite ; positive too late.

Intradermal test : antigen from artificially infected rabbit muscles. Immediate and delayed reactions.

TREATMENT

No specific. Intravenous calcium gluconate in stage of invasion. Injection of convalescent serum controls toxic features. Subcutaneous injection of *carvasept* (preparation of thymol) in olive oil has given some results in U.S.A. Parathyroid—vitamin D—calcium treatment aims at calcification and death of parasites.

Prophylaxis.—Destruction of rats ; inspection of pork, especially sausages. Prohibition of bear meat (U.S.A., Russia). Areas with highest proportion of garbage disposal to pigs give highest trichiniasis rates.

FILARIASIS

Group of diseases due to invasion of lymphatic system or connective tissues by nematode worms—Filariidæ—producing living embryos in blood or tissues and conveyed by biting insects.

1—*Wuchereria bancrofti* (*Filaria bancrofti*.)

Most important ; produces most profound pathological changes.

GEOGRAPHICAL DISTRIBUTION

Wide tropical and subtropical. North to Spain in Europe. Charleston, U.S.A., south to Argentine, Transvaal, Queensland. Isolated foci in N. and Central Africa, Egypt, W. Indies, Brazil, Venezuela, Guianas, S. China, India, Ceylon, E. Indies, Pacific Islands.

ÆTIOLOGY

W. bancrofti: thread-like white worm in lymphatic vessels and glands, thoracic duct. Sexes coiled together ; can be separated with difficulty. Dead individuals become cretified.

Male.—40 mm. by 0·1 mm., coiled with corkscrew-like tail, two spicules, (larger, 500 μ), short, thick, proximal and whip-like distal portion ending in hook; shorter (200 μ), grooved on ventral aspect; fifteen pairs of minute sensory caudal papillæ and saddle-shaped thickening of cuticle on posterior wall of cloaca.

Female.—65–100 mm. by 0·2–0·28 mm. ; anterior end tapers, ending in swelling. Rows of sessile papillæ on head ; oral aperture leading to cylindrical œsophagus ; median intestinal tube, one-third to one-fifth of diameter, opens into rectum posteriorly. Tail narrow, abruptly rounded. Vulva 0·8 mm. behind anterior end ; uterus divided into two branches, much coiled, occupying greater portion of body ; two ovaries and ducts extend to within 1 mm. of tail. Eggs in upper uterus enclosed in chorionic membrane, which becomes sheath of living embryos (microfilariæ). These are emitted by viviparous female and travel *via* lymphatics into blood-stream whence they are ingested by mosquitoes.

Embryo (microfilaria).—280 μ by 7 μ; when seen in living state is structureless; details shown when stained. Entire embryo enclosed in sheath permitting of forward and backward movement; longer than embryo: collapsed part trails behind. Middle third contains granular material in primitive intestine "*Innenkörper*." Transverse muscular striation; one-fifth length from head, V-shaped opening, "Anterior V-spot" = Excretory pore. Short distance from tail is second pore ("Posterior V-spot") representing anus or cloaca. In stained specimen body of embryo is composed of closely-packed nucleated cells which stop short of tip of tail. Head end covered by prepuce from which a fang is shot out by living embryo.

Microfilariæ pass with difficulty through peripheral capillaries; less active in day than in night blood; capable of movement and can travel from place to place.

W. bancrofti var. *vauceli.*—New variety. W. coast Madagascar. Microfilaria shorter, 250 μ, absence of two terminal nuclei in tail, shorter cephalic space, genital cells larger, longer excretory pore, granular "inner body," less graceful curves in posture.

Filarial periodicity.—Microfilariæ exhibit *nocturnal periodicity*—*i.e.*, in peripheral blood in larger numbers in night than in day (W. Indies, S. America, N. Africa and China). Maximum concentration: 10 p.m.–2 a.m. In day-time maximum number microfilariæ in lung capillaries. Mechanism of periodicity never satisfactorily explained. Numbers influenced by sleeping; diminish on waking and bodily activity. Reversal of periodicity can be obtained in three days by reversing hours of sleeping and waking.

Nocturnal unsheathed microfilaria now found in monkey (*Cercopithecus*) by Hawking, periodicity like that of *W. bancrofti* in man.

Life history.—Within one hour of entering mosquito's stomach, microfilariæ cast sheath, bore through stomach wall, collect at anterior end of stomach and enter cylindrical portion of mid-gut. Forward transportation effected by reversed peristalsis. Proboscis of mosquito exerts positive chemotaxis on microfilariæ. Mosquito abstracts 10 times number of microfilariæ present than in equal quantity blood.

Microfilariæ enter muscles of thorax and lie between muscular fibres. Within two days they increase in girth; the anal pore enlarges and the excretory vesicle becomes prominent. Nuclear proliferation takes place; then becomes squat "sausage" form; tail absorbed. Mouth and œsophagus apparent from 5th day.

Larva: 0·5 mm. with bulbar œsophagus, elongated and worm-like, moves sluggishly; three caudal papillæ function in progression and facilitate penetration of human skin. On 10th day larval filaria, 1·4 mm., travels forward to head, enters proboscis sheath; found occasionally in abdominal cavity and legs of mosquito. Two or more ecdyses. In high temperature and moisture, development is complete in 10–14 days; retarded by cold to six weeks. Sometimes die in thoracic muscles, when enclosed in chitin-like mummy. When infected mosquito bites man, larvæ, attracted by warmth, break through terminal portion of proboscis sheath (Dutton's membrane), wriggle onto skin, and penetrate puncture caused by stylet of mosquito.

Intermediary hosts.—Complete development of *W. bancrofti* in: *Culex fatigans* (W. Indies, India, Philippines) ; *C. pipiens* (China) ; various other species of Culex in lesser degree—*Mansonioides annulifera* (S. India) ; *M. africanus* (Central Africa) ; *Aëdes togoi* and *A. chemulpœnsis* (Japan) ; various species of anopheles in S. India, China, N. and W. Africa, Dutch E. Indies and Queensland.

Non-periodic variety of *W. bancrofti* in Pacific (*W. bancrofti* var. *pacifica*). In Pacific Islands this form of filariasis universal, but also, rarely, non-periodic filaria in Philippines (possibly also S. Sudan). Microfilariæ and adults morphologically similar to *W. bancrofti*, but microfilariæ in blood in equal numbers by night and day. Does not develop readily in *C. fatigans*, but in *Aëdes scutellaris pseudo-scutellaris*, *A. polynesiensis* and *A. fijiensis*.

2—*Wuchereria malayi*.

GEOGRAPHICAL DISTRIBUTION

Malaya, Dutch E. Indies, Central India, Ceylon, S. China, Korea, Indo-China.

ÆTIOLOGY

W. malayi.—Practically identical with *W. bancrofti;* females indistinguishable. In male, differences in tail papillæ. Spicules more delicate, also lack of transverse corrugations on stout portion of spicule.

Microfilaria quite distinct from that of *W. bancrofti:* 200–250 μ by 5–6 μ; nocturnal periodicity like that of *W. bancrofti* on E. coast of Malaya: non-periodic on W. Chief points of distinction : different posture and enlongated nucleus at tip of tail. Lies closely folded, with head close to tail, irregularly disposed, showing major curves and minor angulations. Nuclei blurred and intermingled. Tail tapers to fine point, cephalic space twice as long as broad. Excretory pore and cell separated. Develops in special mosquitoes of genus *Mansonioides*, crepuscular or nocturnal feeders. Development similar to *W. bancrofti;* terminal nuclei can be distinguished in larva ; more rapid, 6–8½ days. No development in *Culex*, although may complete metamorphosis in species of anopheles, but principally *Mansonioides annulatus*, *M. annulifera*, *M. longipalpis*, *M. uniformis*.

Pathological effects same as *W. bancrofti;* produces mainly elephantiasis of legs.

Prophylaxis.—Eradication of water plants in which mansonioides larvæ develop is effective.

Relationship to W. bancrofti.—Exist together in S. India and Malaya. *W. bancrofti*, urban distribution : *W. malayi*, rural.

Reservoir hosts.—In Malaya, the Kra monkey (*Macaca irus*), the leaf monkey (*Presbytes melalophos*) and Slow Loris (*Nycticebus coucang*) harbour microplariæ of *W. malayi* type, also dog and cat. Adult forms in two latter are identical with human *W. malayi*; also human microfilariæ can be transmitted by *M. longipalpis* mosquitoes to cat. Both these latter animals also harbour a second distinct species of *Wuchereria*—*W. pahangi*—in which the male has distinctive morphological characters, distinguishing it from the human type of *W. malayi*.

Microfilariæ of *W. Malayi* found in cats in Pate, island N. of Lamu, N. Kenya. *W. bancrofti* hyperendemic there in islanders and elephantiasis common. Discovery of *malayi* outside known range significant.

MOSQUITOES CONCERNED IN TRANSMISSION

Culex fatigans (*W. bancrofti*).—Common brown mosquito in tropics and subtropics. Common in houses, breeds in water tubs or any collection of water. Assumes horizontal position on resting. Palpi of female much shorter than proboscis. Scutellum trilobed, each lobe bearing bristles. Eggs deposited in egg-masses or rafts (no floats). Larva in water hangs obliquely downwards; 8th segment drawn out into repiratory siphon with tuft of hairs.

C. pipiens (*W. bancrofti*).—Common house mosquito of E. and N. America and throughout Europe, China and S. Africa. Brownish grey; white bands on abdomen form lateral triangular patches. Lays eggs in polluted water. Bites viciously. Distinguished from *C. fatigans* mainly by character of male genitalia.

Aëdes scutellaris pseudoscutellaris (*A. variegatus*).—(Formerly *Stegomyia pseudoscutellaris*). Intermediary of non-periodic *W. bancrofti* var. *pacifica* confined to Fiji. Diurnal; bites voraciously; also feeds on birds. Distinguished by three parallel white stripes on mesothorax—incomplete white abdominal cross bands. Larva somewhat resembles that of *A. ægypti*. Breeds in water and decaying vegetable matter, shells of coconuts, crevices and holes in trees, bottles and tins. Eggs, larvæ and pupæ withstand desiccation. Adults enter houses—but is not a domestic mosquito. Main haunts: shady bush round villages. Removal of undergrowth creates through draught and abolishes these mosquitoes. Inland variety in Fiji—*A. scutellaris horrescens*. Larva distinguished by prominent abdominal hairs.

Aëdes s. polynesiensis, new species, wide distribution in Pacific Islands; in many only species. Chief vector of *W. bancrofti* var. *pacifica*. Closely resembles *pseudo-scutellaris*. Chief difference in genitalia of male. Basal lobe of coxite simple with setæ extending nearly to base, also minor distinctions in tail of larvæ. Habits similar to above.

Mansonioides.—Genus found in tropical and Central America, Africa, Malaya. Broad, asymmetrical wing scales, white and grey, " salt and pepper." End of abdomen of female curves upwards, so that only 6½ segments are visible dorsally. Eighth segment, retracted, carries row of chitinized teeth on tergite. Larvæ identified by peculiar respiratory siphon adapted for piercing plant tissues, short, conical base ; distinctive black tip with saw edge and ring of retractile hooks. Pupæ distinguishable by form of respiratory horns modified for piercing plant tissues. Usually night biters ; in jungle bite at any time. Eggs laid in batches on leaves of water plants. Larva and pupa force siphon into air-containing plant tissues. Different species have preference for certain water plants : *M. annulifera* and *M. uniformis* favour *Pistia stratiotes*, " water lettuce " ; others, water hyacinth (*Eichornia crassipes*) and swamp grass (*Isachne australis*). Food of larvæ : fine particles of organic matter.

EPIDEMIOLOGY OF FILARIASIS (*W. bancrofti*)

Incidence usually greater in males, but in Guiana more females than males affected. Incidence greatest after twentieth year and rare in children, but microfilariæ found sometimes in infants of 1½ years. Foci of intense circumscribed infection in many countries ; neighbouring localities free.

PATHOLOGY

In many cases those infected with *W. bancrofti* show no signs of disease ; in assessing filarial incidence those who show signs of filarial disease without microfilariæ, added to those with microfilariæ, but without signs of disease, may be 80 per cent. Pathology extremely varied. Microfilariæ apparently harmless. Two main pathological types :—

(1) Varicosity and disease of lymphatics.
(2) Solid œdema.

Specific lesions in lymphatic glands, fibrosis, focal necrosis and giant-cell inflammation, eosinophil infiltration ; microfilariæ held up in glands die and become cretified. Similar changes in vicinity of living, dead, or cretified adult worms, suggesting diffusion of toxin. *Lymphatic varix* by obstruction of main channels ; compensatory lymphatic circulation. Involvement of thoracic duct causes retrograde lymphatic flow (chyluria, chylous ascites). If varix involves scrotum : " lymph scrotum " with enlarged inguinal and varicose groin glands ; microfilariæ usually in lymph as well as in blood. Calcified adult filariæ in lymphatic glands, retroperitoneal tissues, perirenal fat, tunica vaginalis, etc.

Pathology of elephantiasis.—Arms, scrotum, legs, breast ; exaggeration of normal pathology of *W. bancrofti*, involving fibrotic constriction of all afferent lymphatics draining the part ; regarded as example of hyperfilariation—all mature filariæ having died out. Therefore no embryós in blood. Exact connection between *W. bancrofti* and filarial elephantiasis difficult to prove, but evidence now very strong. Distribution of filariasis and filarial elephantiasis correspond. No essential distinctions in microscopic pathology between filarial elephantiasis and that of congenital, toxic or streptococcal origin. Lymphangiography with diffusible dye—patent blue V—11 per cent. in distilled water, shows distorted, dilated, and varicose lymphatic channels (Kinmouth).

Pathology of non-periodic *W. bancrofti* **and** *W. malayi*.—Similar; former may produce elephantiasis of arm, latter of legs.

CLINICAL FEATURES

Varied manifestations: lymphangitis, filarial abscess, arthritis (hip-joint), synovitis, varicose groin or axillary glands, lymph scrotum, orchitis, funiculitis, hydrocele, chylous hydrocele, elephantiasis of legs, scrotum, vulva, arm, mamma and other parts, chylous diarrhœa. Retroperitoneal suppuration ("filarial abdomen") may be fatal. General tendency to superinfection with pyogenic streptococci, leading to septicæmia and death.

Ascending lymphangitis.—Common early sign of filarial disease; red streaks, usually in legs, cord-like swelling of lymphatic vessels and glands. Usually rigor, pyrexia, pain, headache, vomiting; lasts for several days. Internal lymphangitis produces same train of symptoms and rigor—often mistaken for malaria. Retroperitoneal lymphangitis simulates acute abdomen. Liable to secondary streptococcal infection. Recurring attacks predispose to lymph stasis and eventually to elephantiasis and "elephantoid fever."

Filarial abscess.—Adult filaria may be injured or die as result of lymphangitis, becomes secondarily infected, forms nucleus of abscess, generally deep seated in muscle, but often at site of lymphatic glands of groin, axilla or epitrochlear region. Dead filariæ often found in abscess cavity.

Varicose groin glands.—Commonly with lymph scrotum and chylous ascites, or chyluria. Enlarged, hard, fibrotic inguinal glands in bed of distorted varicose lymphatics; usually transmit impulse on coughing—not to be mistaken for femoral hernia. Often associated with funiculitis and filarial hydrocele. Puncture of glands and aspiration of lymph reveals microfilariæ. Filarial varices on abdominal surface, axilla, legs, arms and spermatic cord often contain live adult filaria.

Glandular enlargement.—Especially associated with non-periodic Pacific form. There enlargement and fibrosis of epitrochlear glands common.

Lymph scrotum.—Skin silky to touch, contains number of lymphatic varices which exude lymph, often with microfilariæ. Associated with enlarged inguinal glands.

Chyluria.—Result of rupture of lymphatic varix into bladder; chyle in urine, which is milky, contains 1·8–2·6 per cent. of fat, albumin, fat globules, lymphocytes and often microfilariæ and blood (hæmatochyluria). Associated with periodic *W. bancrofti*, rarely with non-periodic form. Chyluria attended with suprapubic oppression, pain and general debility.

Lymphuria.—Due to lymphatic obstruction in renal tract by calcified filariæ. Urine cloudy, contains lymphocytes and albumin.

Chylous hydrocele : and hydrocele ; fluid often contains microfilariæ. Other signs of filarial disease present.

Filarial orchitis.—Acute onset, usually with epididymitis and hydrocele, pyrexia, rigor and leucocytosis.

Filarial synovitis.—Hip or knee, with pyrexia, pain, adenitis ; very often secondary suppuration.

Septic complications.—Usually streptococcal, common accompaniment of filarial lesions, may result in septicæmia.

Filarial elephantiasis.—Most frequently in heavy filariated countries. Ninety-five per cent. of legs and scrotum, less frequently arms, mamma, vulva. Usually result of repeated attacks of lymphangitis. Calcified filariæ in deeper tissues demonstrated by X-rays. Lymphatic glands draining area enlarged. Elephantiasis of scrotum may attain enormous proportions and incapacitate patient.

DIAGNOSIS

By discovery of microfilariæ in blood (thick-drop method), not always present in advanced filarial disease. Knott's method venipuncture, 1 c.c. blood in 9 c.c. of 2 per cent. formalin in distilled water ; centrifuge microfilariæ in deposit. By eosinophilia, 15–20 per cent. By lymphatic gland puncture (p. 26): microfilariæ in lymph. Section of gland at biopsy : demonstration of dead or calcified filariæ.

Complement fixation test as in schistosomiasis (p. 196); antigen prepared from dog filaria, *Dirofilaria immitis*.

Intradermal test.—0·25 c.c. of 0·1 per cent. extract of *D. immitis* as antigen. Immediate and delayed reactions ; more reliable for *L. loa* than for *W. bancrofti* infections. Not reliable in later stages of filarial disease or in elephantiasis.

TREATMENT

Hetrazan (*Banocide*) (1-diethylcarbamyl-4-methyl-piperazine hydrochloride) exerts an immediate action upon the microfilariæ in the blood circulation, though it does not affect those in closed cavities of the body, such as hydroceles. Hawking thinks that is opsonizes the microfilariæ, which are subsequently devoured by leucocytes. The evidence now is considerable that it banishes microfilariæ, periodic and non-periodic, from the bloodstream for as long as six months. It has still to be proved that its effects are permanent or that in the long run it destroys the parent filariæ. So far the evidence is unsatisfactory. Regardless of dosage a marked reduction of microfilariæ in the blood results within the space of 2–4 days. Side reactions are few, headache, nausea, vomiting and sometimes skin rashes. In Virgin Islands 90·6 per cent. reduction claimed. The dose is about 2 mg. per kg. three times daily for three weeks. The maximum dose is about 300 mg. for an adult male daily, but 150 mg. daily also appears to be efficacious. When injected intramuscularly microfilariæ disappear from the blood within a few minutes.

Cortisone in advanced elephantiasis. Improvement is due to anti-inflammatory action of drug in reducing lymphatic blockage. In most cases it is advisable to apply bandage therapy with the addition of Unna's paste which has the advantage of reducing the œdema. The dose advised is 100 mg. daily, in divided doses over a period of 30 days or longer. Total period of treatment 7–10 months.

Lymphangitis.—Rest, cooling applications, injections of adrenaline (1 : 1,000) relieve pain and alleviate condition. Recently good results reported from sulphapyridine and proseptacine treatment.

Chyluria.—Rest in bed, foot of bed elevated ; wash out bladder with boracic acid ; introduce into bladder styptic solution :—

Liq. adrenal. 1 : 1,000	1 oz. (29·5 c.c.)
Zinc. sulphat.	5 gr. (0·324 gm.)
Lot. acid. boric. ad	10 oz. (295 c.c.)

Operative measures.—Reserved for elephantiasis. *N.B.*—Varicose groin glands must not be removed or lymphous fistula and elephantiasis result.

Elephantiasis of leg.—Elevation of limb, elastic bandage. *Lang's operation:* deep lymphatic drainage, stripping periosteum of femur, bone trephined, strips of fascia inserted. *Kondoleon's operation:* free incision into fascia lata, removal of strips of aponeurosis ; often temporarily successful.

Elephantiasis of scrotum.—Removal of scrotum, elastic webbing applied to express blood, penis exposed. Testes and cord separated, hypertrophied gubernacula divided. Results successful ; generally no recurrence ; mortality less that 5 per cent.

Elephantiasis of arms.—Removal of strips of tissue.

Elephantiasis of mammæ.—Removed successfully.

Drug treatment.—Disappointing. Recently intramuscular injections of anthiomaline recommended (see p. 197) ; also injected into enlarged glands. Good results claimed in arresting elephantiasis. Effect on microfilariæ not demonstrated.

Prophylaxis.—General anti-mosquito measures and DDT; mosquito nets. In Pacific Islands, clearing undergrowth and creating a through draught blows away mosquitoes. In Malaya and S. China, clearing plants in waterways—especially *Pistia stratiotes*—successful. Subjects of filariasis with microfilariæ in blood are a danger to community.

LOA LOA FILARIASIS (Loasis)

Mostly in W. Africa ; parasite of connective tissue characterized by Calabar swellings and appearance of filariæ under skin and in conjunctiva of eye.

GEOGRAPHICAL DISTRIBUTION

W. Africa; Sierra Leone to Angola, especially the Cameroons in rain forest, mostly along courses of big rivers; far inland up Congo, 1,500 miles; also S. Sudan (Bahr-el-Ghazal).

ÆTIOLOGY

Loa loa, " Eye worm." Stouter than *W. bancrofti*, with chitinous bosses on cuticle, more numerous in female. Mouth unarmed, no papillæ. When dead, often becomes cretified. Embryo maintains diurnal periodicity in blood, in contrast to nocturnal periodicity of *W. bancrofti*. Loa loa found also in forest monkeys of the rain forest in Cameroons. Some of these are identical with that of man and are transmissible to him. Others are not. Seemingly a biological problem comparable with that of *W. malayi* (see p. 222).

Male.—30–34 mm. by 0·35–0·43 mm. ; tapers to tail, which curves ventrally, with two lateral expansions of cuticle. Ano-genital orifice 0·08 mm. from tail tip with two unequal spicules, four globular pedunculated papillæ, one pair small postanal papillæ.

Female.—20–70 mm. by 0·5 mm. ; posterior attenuated, broadly rounded. Vulva 2·5 mm. from anterior extremity. Two long uterine tubes, contain eggs in all stages. Reproduction ovo-viviparous. Embryos develop within egg envelope and uncoil themselves on expulsion from vagina.

Embryo (microfilaria).—298 μ by 7·5 μ ; in fresh blood impossible to distinguish from microfilaria of *W. bancrofti*; in stained films assumes stiff, angular attitude, tail disposed in series of sharp flexures, nuclei of central column of cells larger and extend into tip of tail. Large genital cell at beginning of posterior third. Strictly diurnal ; inversion of periodicity effected gradually as on voyage round world. Sometimes embryo not found in blood for 6–7 years from date of infection.

Life history.—Stages similar to those of *W. bancrofti* in thoracic muscles, connective tissue and fat body of blood-sucking, day-biting " mangrove flies," *Chrysops silacea* and *C. dimidiata*, *C. centurionis* and *C. langi* in Cameroons, *C. distinctipennis* in Sudan. Development complete in 10 days; then 2 mm. by 0·025 mm. Three ecdyses. Larvæ congregate in head in large numbers at root of proboscis sheath when fly feeds, then enter skin as in *W. bancrofti*. In S. Nigeria 3·5 per cent. wild chrysops naturally infected. In human host larva enters connective tissue and migrates. Development very slow, may be several years. Adults numerous in body; long-lived (17 years).

Intermediary hosts.—*Chrysops*: " Blood-sucking fly " ; females attack warm-blooded animals ; males live on vegetable juices. Eyes large in female, contiguous in male. Antennæ consists of three dissimilar segments. Venation of wings complex. Second longitudinal vein not forked ; markings and blotching of wings. Thorax usually irridescent. Semi-aquatic in breeding habits ; eggs laid near water. Larvæ: slender, cylindrical in water. Pupæ like those of Lepidoptera. *Chrysops dimidiata* very abundant in W. Africa (Nigeria, Cameroons). Face and palpi yellow, thorax black with yellow stripes. Abdomen and legs yellow and dusky-brown. Distal half of wings smoky. *C. silacea*, as above, but with abdomen red or bright orange.

PATHOLOGY

L. loa migrates to subcutaneous tissues, under skin, especially conjunctiva, attracted by warmth. No marked blood changes except eosinophilia which is persistent, marked, 30–60 per cent.

CLINICAL FEATURES

Mainly due to migrations of adults; pricking and creeping sensations. Calabar swellings—diffuse œdematous swellings of arms, legs and face. Allergic (reproduced by injection of extract of worms), evanescent, recurring at regular intervals, sometimes accompanied by appearance of worm under skin. Microfilariæ may or may not be found in blood. Cyst-like swellings sometimes contain adults. Found at operation for hernia, etc. Worms in eye cause conjunctivitis, photophobia and irritation. Urticaria, pruritus and allergic papular dermatitis sometimes.

DIAGNOSIS

By microfilariæ in blood (thick drop) usually numerous; also eosinophilia, complement fixation and intradermal tests as in *W. bancrofti*; latter usually more marked (see p. 225).

TREATMENT

No specific treatment. Palliative to Calabar swellings; reduce by evaporating lead lotion. Desensitization by injections of filaria antigen (made from *Dirofilaria immitis*) extract in saline. Removal of adult worms from conjunctiva under novocaine anæsthesia. (Does not necessarily remove infection.)

Hetrazan (see p. 225) has given more satisfactory results in this than in any other form of filariasis. In several instances the adult loa parasites have been found dead or partially cretified under the skin after a course of treatment and Calabar swellings have subsided; but in others they have returned. The dose given by the mouth for 7–11 days in doses of 3–6 mg. per kg. The initial dose on the first day should not be less than 3 mg. per kg. The total amount of hetrazan in an adult man ranges between 17 and 26 gm.

OTHER FILARIÆ

Mansonella ozzardi (*Filaria ozzardi*)

W. Indies, S. America, N. Argentine, amongst aborigines (now considered identical with *F. demarquayi*); adult found in omental tissues.

Male.—32 mm., tail coiled, one spicule.

Female.—65–81 mm. by 0·25 mm. ; two prominent papillæ on caudal extremity ; terminal thickened cuticle.

Microfilaria.—173–240 μ by 4–5 μ, closely resembles *A. perstans* but has sharp tail.

Life history.—Intermediary insects are midges, *Culicoides furens* and *C. paræensis*. Microfilariæ develop in thorax, 7–8 days ; larva in proboscis, 0·78 mm. ; two ecdyses. (For description of Culicoides, see below.)

Acanthocheilonema perstans (*Filaria perstans*).

In man and chimpanzee, Central Africa, Gold Coast, Sierra Leone, Nigeria, N. Rhodesia, Uganda, Venezuela, Trinidad. Guianas, N. Brazil and N. Argentine, in association with banana plantations. In West Africa commonly associated with *L. loa*. Adults long, cylindrical, smooth. Tail incurved in both sexes, chitinous covering gives " mitred appearance." In mesentery, perirenal tissue and pericardium. Causes no tissue, possibly allergic, reactions.

Male.—45 by 0·06 mm. ; head 0·04 mm. in diameter ; cloaca with pre-anal and postanal papillæ. Two unequal spicules.

Female.—70–80 mm. by 0·12 mm. ; head club-shaped ; vulva 1·2 mm. from head.

Microfilaria.—Unsheathed, contractile, measurements vary, 90–110 μ by 4 μ. Small microfilaria with abruptly rounded, tapering tail extending two-thirds of length. Locomotes freely in blood, in heart, lungs, aorta and large vessels.

Life history.—Develops in midges, *Culicoides austeni* and *C. grahami*. Development in thoracic muscles as in *W. bancrofti* ; in 6–7 days larval filaria (0·7 mm.) emerges from proboscis. Seven per cent. of wild-caught midges infected in endemic areas.

Clinical features.—Nil.

Treatment.—Hetrazan has some effect upon microfilariæ perstans in doses of 5 mg. per kg., but reports conflicting.

Culicoides.—Small blood-sucking gnats. Antennæ plumose in male: pilose in female, but long and thread-like. Bite voraciously at dusk or night. Wings contain pigment in membrane, not scales. Eggs laid in shallow water. Larvæ : red " blood worms " with four pairs of gills ; feed on algæ. Adult emerges in 3 days.

Depetalonema streptocerca, formerly known only from the microfilariæ which was named *Agamofilaria streptocerca*. It is probably a parasite of the chimpanzee and the adults are present in the connective tissues and are closely related to *A. perstans*. The microfilariæ (215 μ in length) are found in the corium of the skin and are distinguished by the " walking-stick " handle of the tail extremity and by four prominent nuclei there. Develops in *Culicoides* sp. and is susceptible to hetrazan.

ONCHOCERCIASIS

Onchocerca volvulus, " blinding worm." Filaria parasite producing nodules in skin, often eye lesions and blindness.

GEOGRAPHICAL DISTRIBUTION

W. Africa (Sierra Leone to Angola), Congo, N. Kenya, S. Sudan. Tanganyika, Mexico, Guatemala, C. America, mostly in well-watered districts in vicinity of trees and forests. In Guatemala on coffee plantations 3,000 ft.

ÆTIOLOGY

O. volvulus (*Filaria volvulus*) : white, filiform, with cuticular striations tapering at both ends, female longer ; four males and two females in every tumour.

Male.—20–40 mm. by 0·2 mm. Tail is slightly spiral, bulbous at tip. Two pairs of pre-anal, post-anal and intermediate papillæ ; two unequal spicules, one with fluted end.

Female.—60–70 cm. by 0·4 mm. Head round, truncated ; tail curved ; cuticular striations not so marked as in male, ovo-viviparous.

Egg.—With striated shell ; pointed process at each end (like oranges wrapped in tissue paper), 30–50 μ.

Microfilaria.—300 μ by 8 μ, sheathless. In fluid cyst cavity, lymph glands, surrounding skin, very rarely in blood. Often in healthy skin in vicinity of eyes, and in cornea. Two types, larger and smaller. Body tapers and ends in sharply pointed, recurved tail. Thickening of cephalic cone at commencement of nuclear column.

Life history.—Development in simulium, " buffalo gnat." Abstracts microfilariæ from deep layers of skin near nodule ; they enter stomach, pierce walls, and pass to thoracic muscles, where they develop for 7 days. Larva with two caudal papillæ, 0·45–1 mm., then found in proboscis. Simulium, day-biting fly, 2–6 per cent. naturally infected in endemic areas in Africa ; 11 per cent. in Guatemala.

C. Africa	*S. damnosum, S. neavei*
C. and S. America	*S. avidum* *S. ochraceum* *S. mooseri*

Simuliidæ.—Small black flies, 1–8 mm., with blade-like piercing month parts in female. Characteristic is prominent hump caused by development of scutum, reduction of prescutum. Antennæ, 10–11 joints. In female, eyes separated ; closely set and prominent in male. Wings broad, irridescent. Distinct *alulæ*. Found in enormous numbers in favourable localities in spring and early autumn. Breed in running water. Eggs laid in masses ; larvæ in 2–3 weeks. Attach themselves to stones, weeds, etc. Controlled by DDT. Complete success obtained in Leopoldville and also in Kenya where larvæ of *S. neavei* are transported attached to crabs (*Potamon niloticus*), "phoretic association."

PATHOLOGY

Peculiar subcutaneous, fibrous tumours, size of pea to pigeon's egg. One or several, on parts of body in which lymphatics converge : axilla, popliteal space, elbow, suboccipital region and intercostal spaces. Considerable pain. In S. America in occipito-frontal and temporal regions in association with eye symptoms. Tumours on scalp measure 6–30 mm. ; easily enucleated. Dense mass of connective tissue, mostly made of coiled-up bodies of females embedded in stroma. May give rise to neoplasm. Usually without symptoms, but may produce epileptiform attacks.

Lymphatic enlargement of the scrotum, hydrocele, enlarged testes and elephantiasis of legs reported with microfilariæ in skin. Elephantiasis of scrotum less œdematous than that of *W. bancrofti*. Acute arthritis reported with microfilariæ in synovial fluid.

Skin rashes.—Erysipelatoid rashes (*Erisepela de la costa*). Common in C. America; xeroderma "lizard skin," lichenoid eruption; especially in Europeans ; skin thickened and wrinkled ; causes peculiar enlargement of pinna of ear. Deep-seated onchocerca nodules found usually, but not always.

Eye lesions.—Microfilariæ in cornea and choroid (corneal microscope). Keratitis punctata typical : photophobia, xerosis, impaired vision ; ultimately complete opacity (pannus) of cornea and blindness. Usually associated with erysipelatoid inflammation of face, neuralgia and pyrexia. The greater the distance between the eyes and location of adult filariæ the later will eye lesions develop.

DIAGNOSIS

Biopsy of skin : saline solution, centifruge at 37° C., demonstration of microfilariæ in deposit ; also in scrapings of skin by Thiersch razor. Blood : moderate eosinophilia. Excise tumour and cut section to show adult onchocerca. Intradermal and complement-fixation tests as for *W. bancrofti*.

TREATMENT

Excision of tumours, "denodulization," in early stage said to arrest progress of eye or skin symptoms. Intravenous injections of neostibosan, as for kala-azar, have been tried (see p. 27), but results inconclusive. *Hetrazan* used in Mexico and Guatemala on the whole with good results, the great drawback being the serious character of some of the side reactions due to the destruction of microfilariæ in the skin. Herxheimer-like reactions have been recorded with large doses, although the embryos rapidly disappear from the skin, no proof has, as yet, been forthcoming upon its effects on the adult onchocerca, which apparently escape unscathed. *Antrypol* (suramin) more suitable than hetrazan. Total dosage 160 mg. per kg. or 1 gm. at weekly intervals for 10 doses. Thought to be lethal to adult worms. Combined treatment—preceded by hetrazan 6 mg. per kg. daily for 28 days. *Antihistamines* and *cortisone* applicable for allergic reactions.

DRACONTIASIS—GUINEA WORM

(*Dracunculus medinensis*)

Common parasite of man in India, Persia, Arabia, Sudan, W. Africa, (especially Gold Coast), N. Rhodesia, West Indies, Brazil, Guiana.

Common parasite of carnivora in Africa ; in N. America in fox, racoon and mink, but not in man.

ÆTIOLOGY

Female.—*Dracunculus medinensis*: two feet in length ; thickness of knitting-needle (32·5 cm. by 1·5–1·7 mm.). Lives in connective tissues, harmless till parturient. "Geotropism": drawn to earth—to fingers, toes, scrotum, female breasts ; 90 per cent. migrate to feet (external malleolus). Body cylindrical, smooth, white. Tip of tail pointed, forming blunt hook. Head rounded, terminating in thickened "cephalic shield." Single-bulbed œsophagus. Worm mostly occupied by double uterus containing embryos. Double ovary at posterior extremity. Secretion from head glands irritating, blisters skin. Vulva is small tube in centre of worm. When douched with water, contraction forces uterine contents forward, thickened cuticle gives way and cap is blown off. Uterus then extruded, bursts and viviparous embryos are shed into water. Worm then dies, often becomes cretified, but sinus containing dead worm becomes septic ; may coil round tendons and break.

Male.—Very scarce, has never been found in man, but in experimental dog ; 2·1–2·9 cm. ; equal spicules, 490–730 μ. Lives in between muscle layers of groin. Copulates in deeper tissues, then dies.

Embryo.—651–750 μ by 17 μ. Transverse striation of cuticle ; flattened long slender tail ; rounded head ; bulbous œsophagus. Two glands at root of tail. In water does not swim, but coils up, with side-to-side lashing of tail and tadpole movements of body. In water 6 days ; in mud 2–3 weeks ; then swallowed by water-flea, *Cyclops*, when coiled up—*Cyclops quadricornis* or allied species. Jerky movement of embryo attracts cyclops (like trout and fly). Tail penetrates gut wall, migrates into body cavity, feeds on ovary or testes of cyclops ; 2–3 ecdyses. Then tail absorbed, cylindrical, posterior extremity trilobed ; 4–6 weeks development. Cyclops then swallowed by man. Cuticle dissolved by gastric juice ; larva emerges. Development into adult occupies one year.

Epidemiology.—Limited to certain localities by species of cyclops, wells, etc. (well-water frequently in Indian villages : 38 per cent. cyclops infected). Rhythm of infections : one to two months in year, January and February in Gold Coast (Ghana). Infected cyclops lie at bottom of well ; therefore more people infected in dry season when wells are partially empty.

PATHOLOGY AND CLINICAL SYMPTOMS

Female guinea-worm travels to feet and parts of body in contact with water; in water carriers of India appears on back. May die at any stage, cause sterile abscess or become calcified. Appearance on surface of body preceded by allergic symptoms : fever and urticaria, vomiting, diarrhœa. (Similar symptoms produced by injection of extracts of worm.) Cellulitis as result of injury to or rupture of worm ; œdema, secondary streptococcal invasion, arthritis, synovitis, epididymitis, tendinous contractions ; ankylosis of joints ensues. Guinea-worms found at operation in hernial sacs, etc. Leucocytosis in early stages of infection ; in allergic stage marked eosinophilia ; later may be none.

DIAGNOSIS

Worms seen or felt under skin. Injection of 10 per cent. collargol renders them opaque and visible by X-rays. When calcified easily demonstrated. Eosinophilia.

Intradermal test with extract of dried worm gives positive wheal with outrunners.

TREATMENT

Native custom : make worm protrude from aperture in skin by douching and then gradually wind out on stick ; requires time and patience ; worm usually ruptures and cellulitis results. When located by X-rays can be dissected out.

Bichloride of mercury method.—Aspirate blister fluid with syringe ; worm injected under skin with 1 : 1,000 bichloride of mercury solution, gradually dies and can be extracted gradually. Injection of 9 min. of 1 : 1,000 adrenaline prevents allergic symptoms.

Specific treatment.—Phenothiazine specific for *D. medinensis*. Injected in oily solution 4 gm. (61·6 gr.) intramuscularly at weekly intervals. Two courses sufficient. Finely powdered phenothiazine is emulsified with adeps lanæ and olive oil. Each injection consists of 10 c.c. of the emulsion (phenothiazine 1 gm.) at body heat at some distance above and below site of the worm—two on extensor and two on flexor aspect (if in leg). Site of injection massaged for 5 minutes. Sites are anæsthetized by injection of 3 per cent. novutox (procaine and adrenaline solution). At least 1 gm. (15·4 gr.) of phenothiazine injected in vicinity of buried worm. After 5–7 days the worm may be extracted by rolling stick method. In massive induration or sinus, injection is made directly into area. Sinus dries up and worm massaged out by pressure. No toxic symptoms noted. Penicillin for secondary infections.

Prophylaxis.—Protecting wells or drinking water from pollution by guinea-worms. Adding potash to water or raising temperature by portable steam generator kills cyclops. In Mysore, where step-wells are source of infection, introduction of barbel fish, which feed on cyclops, has been effective. Wells also treated every 14 days with *perchloron* (bleaching powder substitute).

CHAPTER XV

METAZOAL DISEASES

CESTODES (Tapeworms)

Communal segmented worms. Head develops independently from embryo. Segments = strobila ; musculature relieves strain on head. Each segment (proglottis) hermaphroditic, male elements fertilize female of adjacent segment, former develop first. Nutriment absorbed through cuticle. Live for several years.

1. **Pseudophyllidea,** with slit-like suckers and grooves (bothria).

"BROAD TAPEWORM":

Diphyllobothrium latum; Dibothriocephalus latus.

Geographical distribution.—In small intestine of man, dog, cat, bear, walrus, sea lion, fox, mongoose, mink, pig. Sweden, Russia, other European countries, Turkestan, Japan, Madagascar, Central African lakes, recently U.S.A. (L. Michigan).

Ætiology.—*D. latum* : long, broad, flat tapeworm ; grey, translucent ; may attain 10 metres. Coiled in small intestine. Scolex, 3 mm. ; two slit-like suckers, thin neck ; 3–4,000 proglottides. Genitalia complicated, "rosette-shape" twisting of uterus. Dorsal aspect contains main male elements : ventral female. No segments passed in fæces.

Egg.—Brown, operculated, 70 μ by 45 μ, in fæces in large numbers ; yolk cells tightly packed.

Life history.—Egg passed in water. Operculum lifted, ciliated, hooked onchosphere or coracidium (22–30 μ) emerges: resembles ball. Swims by cilia; dies in 24 hours. Swallowed by freshwater crustacea ("water fleas," *Cyclops strenuus, Diaptomus gracilis, D. oregonensis,* U.S.A.), hooks tear hole in intestinal wall (may kill Cyclops). Outside gut becomes *procercoid,* 50–60 μ, with terminal spherical appendix with six hooklets (as in onchosphere) ; then swallowed by *second intermediary,* fish : pike, perch, salmon, trout, grayling, barbel in Africa; pike, wall eye, burbot in U.S.A. Procercoid penetrates stomach after 3–4 days ; in body cavity encysts as *plerocercoid* (or sparganum), 6 mm., in muscular and connective tissues, then eaten with roe (caviare) or insufficiently cooked fish and develops in 5–6 weeks into adult *Diphyllobothrium.*

Clinical features.—Symptoms usually trifling. In small percentage produces severe anæmia (of pernicious type). Dried or alcoholic extract of worm causes destruction of r.b.c., but not proportionally of hæmoglobin. Anaemia caused by absorption of vitamin B_{12} by worm in intestine.

Diagnosis.—Usually easy by very numerous eggs in fæces.

Treatment.—Worms easily expelled by *Filix mas* (p. 237), **tetrachlorethylene or oleoresin of aspidium.**

D. minus, claimed by Russians as separate species, from L. Baikal. Life history similar ; second intermediary : different species of salmonidæ, lavaret, grayling, etc.

Diphyllobothrium mansoni

Adult in dog : *plerocercoid* or *sparganum* in man, dog, wolf, fox, cat, leopard, tiger. Japan, China, E. Africa, Australia, British Guiana. Resembles *D. latum* ; 6–10 m. ; more delicate structure ; egg narrower and ellipsoid. Plerocercoid (*Sparganum mansoni*) in man occasionally in kidneys, iliac fossæ, pleural cavity, urethra, subcutaneous tissues.

Ocular sparganosis.—In Tonquin, Japan, China, worm in orbit ; pain, redness, œdema of eyelids, lacrymation. (Treatment by tarsorrhaphy.) Under natural conditions in frog, *Rana nigromaculata*, or snake, *Elaphe climacophora* ; probably contracted by man through Chinese practice of applying split frogs as poultices to sores on hands.

Life history.—As in *D. latum* ; first intermediary, *Cyclops leuckarti*.

Spirometra mansonioides

May attain length of 1 m. by 5 mm. Adult in intestine of cat. Life history probably similar to above. Larval stage : *Sparganum proliferum*. In man, plerocercoids in large numbers in walls of alimentary canal, mesentery, kidney, lungs, heart, brain. Japan, Florida.

Body of cyst contains calcareous corpuscles, easily enucleated, but prognosis grave owing to numbers.

OTHER RARER TAPEWORMS

Raillietina celebensis, *R. madagascarensis* and *R. quitensis* found rarely in Siam, British Guiana, Mauritius, Formosa and Ecuador. Numerous " coalhammer " hooklets on suckers and rostellum, unilateral genital pores on proglottides. Ripe segments contain egg capsules. Ovoidal eggs possess large hooklets. Usually parasites of birds and rats.

Inermicapsifer arvicanthidis and *I. cubensis*. In Kenya, Congo and Cuba. Recently shown by Fain to be identical. In Central Africa normally parasites of hyracoidea and rats. Probably imported by African rodents to Cuba.

2. **Cyclophyllidea.**—Round suckers : genital orifice marginal.

" PORK TAPEWORM ": *Tænia solium*

Geographical distribution.—Co-extensive with pig. Unknown in Mahommedan and Jewish countries. In upper third small intestine.

Typical tapeworm, 2–3 m. (exceptionally, 8 m.). Head globular, quadrangular, 1 mm. in diameter. Rostrum short, pigmented with double row of hooklets ; four projecting suckers. Mature proglottides, 12 mm. by 6 mm. ; each has *marginal* genital pore. Uterus median, with 7–10 *stout diverticula*. Terminal segments in fæces show independent movement and migrate outside anus.

Egg.—31–56 μ, round, two radially striated shells ; contains six-hooked onchosphere.

Life history.—Mature segments in fæces pass out and are eaten by pig. Man occasionally infected (cysticercosis). Onchosphere penetrates gut and enters blood ; then, in muscles, loses hooks and becomes *Cysticercus cellulosæ*. Pork infected is " measly pork."

In alimentary canal, bladder is absorbed by gastric juice. Head, evaginated, passes to small intestine where scolex fixes itself to gut wall and forms proglottides.

Clinical features.—Usually no symptoms. In debilitated and in children may cause gastro-intestinal disturbance, possibly anæmia.

Treatment.—See p. 237.

CYSTICERCOSIS

Accidental ingestion of eggs of *T. solium* ; man serves as intermediary host. Onchospheres migrate to muscles of tongue, neck, ribs, lungs, liver, heart and eye and, more especially, brain.

Geographical distribution.—Cysticercosis has been reported from nearly every country, including England. Most extensive infections in British soldiers, especially from India.

Pathology.—Cysticercus in brain surrounded by neuroglia, lymphocytes and few plasma cells ; when dead and degenerated acts as irritant ; focal necrosis around cyst. Then becomes calcified, commencing in scolex ; cyst capsule unaffected. Process may occupy three years or longer.

Clinical features.—Occasionally associated with intestinal infection of *T. solium*. Jacksonian epileptic fits with cerebral cysticercosis ; cyanosis, biting of tongue, incontinence ; sometimes fatal ; may suggest cerebral tumour. Mental degeneration, loss of memory and higher senses.

In muscles cysticerci cause no general reaction ; gradual development of small subcutaneous intramuscular swellings. Sometimes toxæmia and pyrexia. Often cysticercosis diagnosed accidentally by X-ray.

Diagnosis.—Palpable cysts in tissues, size of pea and even larger, up to pigeon's egg. Excise and cut section to show structure of cysticercus : translucent membrane with central " milk spot." Nodules usually appear in crops, sometimes difficult to find.

X-ray examination no use unless cysts are calcified. Then : elongated shadows ; fully calcified cyst has characteristic appearance. Eosinophilia not marked ; no aid to diagnosis. Complement-fixation tests inconclusive.

Precipitin test with antigen from *Cysticercus cellulosæ* sometimes employed. Intradermal Casoni test (p. 240) positive in 50 per cent. No constant change in C.S.F. ; sometimes excess of lymphocytes and eosinophiles; colloidal benzoin reaction sometimes positive.

Treatment.—Rarely successful. Localization of cysticerci in brain by radiography, and removal. Intravenous injections of antimony tartrate useless. Luminal and bromides helpful in controlling fits. If *T. solium* is present in intestine *Filix mas* is indicated.

Prophylaxis.—Regurgitation of proglottides of *T. solium* into stomach suggested; probably from eating sausages made from pigs' intestines or food contaminated by pig excreta. Control of sausage meat indicated. Fæces disposal. Fly control; eggs carried by flies from infected fæces.

"BEEF TAPEWORM": *Tænia saginata*

Geographical distribution.—World-wide, wherever beef is eaten, especially in Abyssinia; multiple infections common. Worm found coiled up in small intestine.

Ætiology.—*T. saginata* differs from *T. solium* in several points, especially absence of rostellum and hooks. Semi-transparent, 4–10 m., 2,000 segments sometimes; *scolex* pear-shaped, 1–2 mm., pigmented, with four lateral suckers and sucker-like organ at apex. Genital pore marginal, at hinder end of proglottis, alternating between right and left margins; 20–35 lateral branches on each side of uterus.

Egg.—30–40 μ by 20–30 μ, indistinguishable from those of *T. solium.*

Life history.—Gravid proglottides in fæces; creep into grass and disintegrate. Eggs eaten by ox. Onchospheres, set free, pass into small intestine, bore through wall, and are carried to muscles, especially pterygoids, diaphragm, tongue.

Cysticerci.—7·5–9 mm. by 5·5 mm.; live 8 months in ox; "measly beef" eaten by man; bladder digested; liberated scolex passes to small intestine and affixes itself by suckers to gut wall.

Clinical features.—May occasionally cause abdominal pain and some anæmia.

Treatment of tapeworm infections.—

Filix mas.—Preliminary starvation two days: tea, toast, fluids +, glucose D. Extract of filix mas, 45–90 min. (2·8–5·6 c.c.) in gelatin capsules. For adult man, 126 min.; for female, 90 min.

No Breakfast—cup of tea at 7 a.m.
8 a.m., 2 capsules of 15 min. *Filix mas.*
8.30 a.m., repeat.
9 a.m., repeat.
Complete quiet; sips of water.
9.30 a.m. *Ol terebinth.* 20 min. (0·124 c.c.) emulsified with gum acacia.
10.30 a.m. Sodi. sulph. ½ oz. (14·7 c.c.)

Directly purging commences give hot-water enema of 1½ pints (assists in dislodging worm and separating head). All stools strained and examined for head. *N.B.*—If head is not found, useless to give further course of treatment till segments again appear in stools.

Atebrin (mepacrine) lethal to tapeworms in doses of 0·9–1 gm. dislodges head of worm. Best given in combination with *Filix* *mas* as above. Also has been injected into duodenum by Ryle's tube.

Anthiphen or *Dichlorophen* (see p. 241) recently introduced. No starvation or purging necessary. Dose for adult 3–6 gm. at 10 a.m. (0·5 gm. for 16 lbs. or 7·25 kg.).

T. saginata more difficult to remove than *T. solium* or *D. latum*.

Pelletierine (alkaloids of pomegranate bark) ; preparation as above.

DWARF TAPEWORM: *Hymenolepis nana*

Geographical distribution.—Subtropics and tropics. Egypt, Sudan, Siam, Japan, S. America, S. Europe, Portugal, Spain, Sicily. In small intestine. *H. nana*, 5–45 mm., 100–200 proglottides. Scolex subglobular ; rostellum with single crown hooklets ; four subglobular suckers.

Egg.—180 in each segment, oval, globular. Two membranes : outer or vitelline, 40–46 μ ; inner, 20–30 μ. Mammillate projection at each pole, enclosing onchosphere and three pairs hooklets. Eggs set free in fæces.

Life history.—No intermediary host. Larvæ enter villi of small intestine and become *cercocystis*.

Clinical features.—In large numbers, hundreds or thousands ; occasionally cause pain, diarrhœa, or epileptiform convulsions due to toxæmia.

Treatment.—Not dislodged by *Filix mas*. Chloroquine or Camoquine in full doses—0·25 gm. three times daily for 7–10 days now claimed to be effective.

Hymenolepis diminuta

Resembles above; parasite of rats and mice. In man in Spain, Italy, S. America, Congo, W. Indies, Iraq.

20–60 cm. by 3·5 mm. ; head small, cuboidal ; median anterior invagination forms cavity into which pyriform rostellum retracted ; four unarmed suckers. Proglottides increase in size, broader than long.

Egg.—Circular, 60–80 μ. Outer shell yellowish, thickened ; indistinct radiations containing hexacanth onchosphere.

Life history.—Cysticercus stage in body cavity of various insects : fleas (*Xenopsylla*), larval meal-worms, beetles, moths. Rats parasitized by eating infected fleas.

Clinical features.—Does not produce any special symptoms. Treatment with chloroquine as above, but *Filix mas* treatment also efficient.

Dipylidium caninum

Common parasite of dog, cat, jackal. A hundred records in man; in small intestine.

15–40 cm. by 2–3 mm. Rostellum retracted into infundibulum, 3–4 circles of hooklets (rose-thorn shape) ; four elliptical suckers. Proglottides narrow ; 200 or more. Two sets of genitalia in each segment. Genital pores symmetrical at lateral margins.

Egg.—Round, 35–40 μ.

Life history.—Cysticerci in dog-louse (*Trichodectes canis*), dog-flea (*Ctenocephalus canis*) and human flea (*Pulex irritans*). Eggs eaten by larval fleas, etc. Infection of man accidental, by swallowing infected fleas.

Clinical features.—No symptoms.

Treatment.—*Filix mas* effective (see p. 237).

LARVAL FORMS OF TÆNIA IN MAN

Hydatid : larva of *Echinococcus granulosus*. (*Tænia echinococcus*.)

Geographical distribution.—Adult is parasite of dog, wolf, jackal, fox, monkey, kangaroo. Common in Iceland, Australia, Arabia, Algeria, Tunis, Egypt, Abyssinia, S. Africa, Argentine, Uruguay.

Larval stage (hydatid) after ingestion of egg by mammal or man; usually in liver.

Ætiology.—*E. granulosus* ; small, 2·5–6 mm., scolex 0·3 mm. ; apex with rostellum and two circular rows of hooks varying in size and number. Proglottides 4 ; terminal longest (2–3 mm.), one sexually mature with 800 eggs. Genital apertures marginal ; one to each proglottis. In small intestine, difficult to remove without breaking head. Eggs passed in dog fæces.

Egg.—Double-shelled, ovoid, 32–38 μ by 21–30 μ ; onchospheres with 3 pairs of hooklets. When swallowed shell is digested and onchosphere escapes to portal vein and liver, also lungs ; embryos filtered out and grow rapidly. In 3 months are 5 cm. in diameter. Hydatid cyst wall : fibrous, laminated layer formed by host : (1) thick, median, striated layer secreted by cyst ; (2) inner germinal layer from which brood capsules and daughter cysts arise. Two types of proliferation : (1) endogenous, (2) exogenous. In former towards cyst-cavity; in latter outwards.

Brood capsules.—From small nuclear masses of parenchymatous layer ; vesicles with larval scoleces. When free in cavity = " hydatid sand."

Daughter cysts.—Inside cyst, formed by injury or mechanical interference from detached germinal layer and from brood capsule cells.

Exogenous cysts.—Daughter cysts in omentum and bones ; rupture of germinal and laminated layers by intracystic pressure.

Alveolar or multilocular type.—Solid, sponge-like tumour ; peripheral infiltration, central necrosis. Found in S. Germany, Tyrol, Württemberg, Russia, Siberia. Vogel has shown that this is distinct species—*E. multilocularis*. The first hosts are foxes, dogs, housecats and intermediary hosts are field-mice, other rodents and, occasionally, man. In arctic alveolar larval phase is found in livers of burrowing mice. *E. multilocularis* differs in that herbivora play no part. Field-mice take up eggs from foxes and larval stages develop in their livers. The adult worm differs in the position of the genital pore which is front of the middle of the proglottis. The number of testes is 21–29 and they lie behind the posterior end. The uterus has no lateral branches. The length of the mature worm is 1·4–3·4 mm.; in *E. granulosus* it is 5–8 mm.

Clinical features.—Dogs infected by eating offal, especially of sheep. Man, by close association with dog. Symptoms vary according to site of cyst : toxæmia, pyrexia, urticaria. In brain : cerebral tumour. In liver, spleen, peritoneum : simulates malignant growths. In lung : compression, fluid in pleural cavity. In kidney : resembles hydronephrosis. Local symptoms in long bones, heart, orbital cavity.

Cyst wall : outer chitinous ; inner germinal with muscular fibres, calcareous bodies and glycogen. Bladder : watery fluid, sp. g. 1007 ; albumin and protein allied to casein. Intracystic toxin, hydatid fluid in abdominal cavity, produces anaphylactic reaction and shock.

Diagnosis.—Cystic swelling, giving " hydatid thrill " ; on puncture yielding hooks and scoleces. Precipitin reaction : equal parts of hydatid fluid and serum in incubator : precipitate forms. Complement-fixation (Wassermann technique) : antigen (0·4 c.c.), from scoleces macerated with alcohol.

Intradermal test (Casoni) : hydatid fluid of sheep or man injected intradermally ; reaction in 10 minutes : large wheal surrounded by erythema. Secondary reaction 8 hours later.

Treatment.—Surgical. In man cysts tend to die and become calcified. Rarely suppurate.

Cænurus cerebralis.—Larval form of *Tænia multiceps* of sheep ; adult in intestine of dog ; rare in man. Causes symptoms of cerebral tumour. *C. glomeratus* : normally in gerbille ; found in abscess of chest wall in Nigeria.

A LIST OF DRUGS EMPLOYED IN THE TREATMENT OF TROPICAL DISEASES

Acidum ascorbicum. *Vitamin C, Cevitamic Acid, Redoxon, Proscabin.*

Enolic form of 3-*keto-1-gulofuranolactone.*

Scurvy, wound healing.

Oral, tab. *acidi ascorbici* 50 mg. (0·7 gr.) three times daily.

In acute cases, intravenous.

Acranil. *Hydrochloride of acridine.*

Giardiasis (Lambliasis), Balantidiasis.

Oral, tab. 0·5 gm. (7·7 gr.) Three tablets daily for five days.

No toxic effects.

Alepol. *Sodium hydnocarpate, or sodium gynocardate.*

Leprosy.

Subcutaneous, intramuscular or intravenous, 1–10 cc. of 1 or 2% solution.

Anabin. *Kurchi-bismuth-iodide.*

Alkaloid of kurchi is *conessine.*

Amœbiasis.

Oral, tab. 0·25–0·65 gm. (3·7–10 gr.).

Aneurin. *Aneurinæ Hydrochloricum B.P., Thiamine Hydrochloride, Vitamin* B_1.

3-(4′ *Amino-2′-methylpyrimidine-5′) methyl-5-B-hydroxyethyl-thiazolium chloride hydrochloride.*

Beriberi, Burns, Varicose Ulcers.

Oral, tab. 3 mg. Injection, 25 mg. (0·37 gr.) in 1 c.c. Store protected from light.

Anthical.

Zinc oxide and anthisan.

Lotion for sunburn and insect stings.

Anthiomaline. *Lithium antimony thiomalate.*

Schistosomiasis, Lymphogranuloma inguinale, Leishmaniasis, Filariasis (*W. bancrofti*).

Intramuscular, 0·5–4 c.c. (1 c.c. = 10 mg. Sb.).

10–20 injections, 2–3 per week.

Anthiphen. (M. & B.) *Dichlorophen.*

2 : 2′-dihydroxy-5 : 5′-dichloro-diphenyl methane.

Tæniasis. *Tænia saginata.*

Oral, tab. 0·5 gm. per 7·25 kg., in one dose at 10 a.m.

Total dosage 6 gm. (92·5 gr.) in three equal amounts at intervals of 8 or 12 hours.

Anthisan.

Antihistamic for allergic conditions in filariasis and schistosomiasis.

Oral, tab. 0·3 gm. (4·6 gr.) increasing to 1 gm. (15·4 gr.) daily in divided doses, with food.

Antimonii et Potassi Tartras B.P. *Tartar Emetic.*

Kala-azar, Oriental sore, Espundia, Yaws, Lymphogranuloma inguinale, Ulcerating Granuloma, Trypanosomiasis, Relapsing Fevers, Lepra reactions, Schistosomiasis.
Intravenous, in solution in distilled water, 0·03–0·12 gm. (0·46–1·8 gr.).
Alternate days—up to total of 2·5 gm. (38·5 gr.).

Antimonyl. a', a'-dimercapto-potassium succinate (*T.W.S.B.*) (Friedheim). Soluble in water—30%.

Schistosomiasis (*S. mansoni*) in Brazil.
Intramuscular injection 0·5 gm. Total 32 gm. for 13 days: 23–42 mg. per kg.
Intravenous 0·7–2·3 gm. total (10·8–35 gr.).

Antimosan. *Von Heyden* 661.

Potassium antimonyl pyrocatechol-sulphonate. Contains 12·5% antimony in trivalent form.

Kala-azar and other forms of Leishmaniasis.
Intravenous or intramuscular, 0·2 gm. (3 gr.), twice weekly.

Antrenyl (Ciba).

2-*diethylaminoethyl-a-cyclohexyl-a-phenylglycollate methobromide.*

Antispasmodic for relief of gastro-intestinal pains.
Oral, tab. 5–10 mg. (0·07–0·15 gr.) four times daily.

Antrycide chloride.

4-*amino*-6-(2'-*amino*-6'-*methylpyrimidyl*-4'-*amino*)-*quinaldine*-1:1'-*dimethochloride.*

Trypanosomiasis of cattle and man.
Injection: single dose of 1 mg. per kg. for *Trypanosoma congolense, T. rhodesiense, T. brucei, T. evansi, T. equiperdum* and *T. equinum.*

Antrypol B.P. *Suramin, Bayer* 205, *Germanin, Fourneau* 309, *Moranyl, Naganol, Naphuride.*

Urea of acid dimeta-aminobenzoyl-meta-aminoethyl-benzoyl-l-naphthylamino-4-6-8 *trisulphonate of soda.*

Trypanosomiasis (*T. gambiense* and *T. rhodesiense*), Onchocerciasis.
Intravenous, or rarely intramuscular, 1–3 gm. (15·4–46·2 gr.). Active in early stages of trypanosomiasis.

Aralis (Winthrop).

Tablets containing 75 mg. of Aralen (chloroquine diphosphate) and 250 mg. of Milibis (bismuth glycolylarsanilate).
The quantities are chosen to give a balanced therapeutic action in both prophylactic and therapeutic treatment of amœbiasis.
Intestinal and extra-intestinal amœbiasis.
Dose. Tab. 6 daily for 7 days.
Prophylactic, 3 tablets daily on 2 days a week.

Areca B.P.C. *Betel Nut.*

Dried ripe seeds of Areca catechu. Contains not less than 25% of arecoline.
Tæniasis.
Oral, powder or emulsion 1–4 gm. (15–60 gr.). Effective in combination with oleoresin of aspidium.
Given as enema 1 : 20.

Arsenamide. *Sodium Thiacetamide.*
p-p(bis-carboxy-methyl-mercapto) arseno benzamide.
Filariasis—*W. bancrofti* and *W. bancrofti* var. *pacifica.*
Intravenous or intramuscular injection, in 2% solution, 1 mg. per kg. daily for 15 days. Average daily dose 0·5 gm. (7·7 gr.). Total 7·5 gm. (185 gr.).

Arsthinol (Balarsen). "*S.T.B.*"
N-2-acetylamino-4-methylol cyclo (ethylene dimercaptoarseno)-phenol.
Amœbiasis, Yaws.
Oral, tab. 10 mg. (0·15 gr.) daily for 5 days.

Ascabiol. *Benzevan, Proscabin.*
Benzyl benzoate.
Scabies, Pediculosis (*P. capitis* and *P. pubis*).
Local application.

Auremetine.
Combination of periodides of *emetine* and *auramine*, containing 28% emetine, 16% auramine and 56% iodine.
Amœbiasis in chronic stage.
Oral, in emplets (enteric-coated tablets) or slipules, 0·12–0·2 gm. (1·8–3 gr.). Total 4 gm. (61·7 gr.).

Aureomycin. *Chlortetracycline.*
Antibiotic from *Streptomyces aureofaciens.*
Undulant fevers, Typhus, Q fever, Lymphogranuloma venereum, Psittacosis, Amœbiasis, Yaws, Coccidiomycosis.
60 mg. per kg. in capsules of 250 mg. (3·7 gr.) four times daily for 5 days. Important that each capsule should be taken with a cup of milk or water. Intravenous or intramuscular, 3 mg. per kg.

Avomine.
8-chloro-theophyllinate of bromethazine.
Nausea, Travel-Sickness, Cholera.
Oral, tab. 25 mg. (0·37 gr.).

Azacrin. *Amino-aza-acridine.*
2-methoxy-6-chloro-9-(5′-diethyl-amino-2-pentyl)-amino-3-aza-acridine hydrochloride.
Malaria, Giardiasis.
Oral, tab. 0·4 gm. (6·1 gr.) for 5 days.

B.15.
(*2 Hydroxy-5-arsonophenyl methane.*)
Amœbiasis and Amœbic Hepatitis.
Oral, 15–65 gm. (231-1,003 gr.) over a period of 10–30 days.
Recommended dosage, 2 gm. (30·8 gr.) daily.

Bacitracin.
Antibiotic from strains of *Bacillus subtilis.*
Amœbiasis.
Oral, tab. 80,000 units for 10 days. Intramuscular, 50,000 units for 7 days. Intravenous contra-indicated. Bacitracin is nephrotoxic.

Bal (Dimercaprol). *British Antilewisite.*

Inhibits metal-containing compounds.

Ampoules containing 100 mg. Intramuscular injections—100 mg. (1·5 gr.) at 4-hourly intervals; 2nd, 3rd and 4th days 100 mg. twice; 5th and 6th days 100 mg. daily.

Berberine sulphate. (India only) *Orisol.*

Oriental sore.
Subcutaneous injection, or as ointment, 0·06–0·3 gm. (0·9–4·6 gr.).

Betanaphthol B.P.

B-naphthol.

Ancylostomiasis, Ascariasis, Tæniasis.
Oral, 0·2–0·65 gm. (3–9·9 gr.).

Bismosol.

10% *solution of potassium sodium bismuthotartrate (containing* 0·3% *piperazine) in glucose solution.*

Syphilis, Yaws.
Intramuscular, 0·1 c.c.

Bismuth oxychloride.

Yaws.
Lupus erythematosus (in 10% ointment).
Oral, 0·6–2 gm. (9·2–30·8 gr.).

Bromoguanidine.

Analogue of paludrine in which a bromide atom replaces chlorine.

Possesses antimalarial properties corresponding to those of paludrine.

Camoform. *Biallylamicol, S.N.* 6771, *P.A.A.* 701.

6 : 6′*-diallyl-a, a′ bis (diethylamino)*-4 : 4′*-bi-o-cresol.*
Allied to camoquine.

Amœbiasis.
Oral, tab. 2 gm. (30·8 gr.) daily for 10–14 days.

Camoquine. *Amodiaquine, S.N.* 10751, *Flavoquine, Miaquin, CAM-AQI.*

7*-chloro-*4(3*-diethyl aminomethyl-*4*-hydroxyanilino) quinoline.*
Malaria, Giardiasis.
Oral, tab. 0·2 gm. (3 gr.) of base as dihydrochloride.
Adults 0·6 gm. (9·2 gr.); children 0·4 gm. (6·1 gr.).
(Each 261 mg. tablet of camoquine contains 200 mg. of base.)

Carbarsoneum B.P.

Amibiarson, Leucarsone, Amabevan.
4*-carbaminophenylarsonic acid.*

Yaws, Chronic amœbiasis.
Oral, tab. 0·25 gm. (3·7 gr.); or by rectum in solution 2 gm. (30·8 gr.) dissolved in 200 c.c. 2% sodium bicarbonate solution as retention enema.

Carbonei Tetrachloridum B.P. *Tetrachlormethane, Tetraform,* CCL_4.

Effective anthelmintic for Ascaris, Ancylostoma and Tapeworms.
Now largely replaced by Tetrachlorethylene.
Oral, in gelatin capsules, 3 c.c. (48·6 min.) maximum dosage.

Chaulmoogra oil.

Oil expressed from seeds of *Hydnocarpus kurzii.*
Leprosy.
Oral, intradermal, subcutaneous or intramuscular, 0·3–5 c.c.

Chenopodium oil. *Oil of American Wormseed.*

Oil distilled with steam from fresh flowering and fruiting plants of Chenopodium ambrosioides var. anthelminticum. Contains 65% *W/W of ascariodole.*

Ascariasis, Ancylostomiasis, *Larva migrans.*
Oral, in capsules or in mixture 0·2–1 c.c.

Chiniofon B.P. *Quinoxyl, Yatren, Anayodin, Dysentulin.*

Sodium-7-iodo-8-hydroxy-quinoline-5-sulphonate.

Amœbiasis, Bacillary Dysentery.
Oral, tab. 0·06–0·5 gm. (0·9–7·1 gr.). Retention enemata 2½–3% solution 1–5 gm. (15·4–77·1 gr.).

Chloromycetin. *Chloramphenicol* B.P. Add.

Antibiotic originally isolated from *Streptomyces venezuelæ.* Now synthetic. *D-(-)-threo-2-Dichloroacetamido-1-p nitrophenyl-1* : 3 *propanediol.*

Typhus fevers, especially Mite typhus and Typhoid, Bartonellosis, Whooping cough, Gonorrhœa.
Intramuscular or intravenous injections 1–5 gm. (15·4–77·1 gr.) daily.
Oral, capsules 750 mg. four times daily for 6 days. May produce aplastic anæmia, agranulocytosis and thrombocytogenic purpura.
Chloromycetin palmitate suspension (P.D. & Co.). Bitterless derivative for treatment of infants and children.

Chloroquine. *Aralen, Resochin, Avlochlor* (I.C.I.).

7-chloro-4(4-diethyl-amino-1-methyl, butyl amino) quinoline diphosphate.

Malaria (powerful schizonticide), Hepatic Amœbiasis, Balantidiasis, Giardiasis, *Hymenolepis nana, Trichuris trichiura.*
Oral, Suppressive for malaria 0·3 gm. weekly. Injection, ampoules of 5 c.c. (equivalent to 40 mg. (0·6 gr.) of base per c.c.). Curative. First day 3 doses of 0·3 gm. followed by one dose of 0·3 gm. daily for 3 days. Dosage in terms of base. Side effects, pruritis of hands, bleaching of hair.

Cinchona B.P.C. *Cinchona Febrifuge.*

Contains mixed cinchona alkaloids in varying proportions.

Malaria.
Oral, tab. 0·06–0·6 gm. (0·9–9·2 gr.) two or three times daily.
Used as a substitute for quinine.

Compound 6257 (Ciba) India.

Condensation product of sulphathiazole and formaldehyde.

Cholera.
Oral, 6 gm. (92·5 gr.). Total dosage 28 gm. (432 gr.) recommended.

Conteben. *Thiacetazonum, Thiosemicarbazone.*
(4-acetylamino benzaldehyde-thiosemicarbazone.)
Leprosy.
Oral. Powder 12·5 mg. (1·8 gr.) to 250 mg. (3·7 gr.).
Maximum 400 mg. (6·1 gr.).
Course of 1 year.

Cortisone ointment.
Seborrhœa. Allergic reactions due to fungus infections of feet (athlete's foot).

Crystal Violet B.P.
Gentian violet, Methyl rosaniline, Hexamethyl pararosaniline hydrochloride.
Oxyuriasis, clonorchiasis, *Hymenolepis nana.*
Oral, tab. 0·5 gm. (77·1 gr.) t.d.s. for 7 days for oxyuris. 18 mg. per kg. 10–20 days for clonorchiasis—total 1·2 gm. (18·4 gr.).

Dapsonum B.P.C. Supp. *D.D.S., Avlosulphon, D.A.D.P.S.*
4 : 4′ *Diamino-diphenyl sulphone.*
Leprosy, Mycetoma, Dermatitis herpetiformis.
Oral, tab. 100 mg. (1·5 gr.) twice weekly.

Daraprim. *Pyrimethamine, Malocide.*
5 (*p-chlorophenyl*)-2 : 4-*diamino*-6-*ethylpyrimidine.*
Malaria, especially benign tertian.
Oral, 10–20 mg. (0·15–3 gr.) or more daily; 5 mg. (0·7 gr.) daily suppressant.

D.B.P. *Dibutylisphthalate B.P.C., Butylphthalate.*
Insect repellent, and more effective than D.M.P. against trombidid mites. Impregnation of clothing 1 oz. to set of clothing (= 30 c.c.).

Diasone. *Promanide, Sulphoxone sodium.*
Derivative of Dapsone.
4 : 4-*Diamino-diphenyl sulphone disodium formaldehyde sulphoxylate.*
Leprosy, Tuberculosis.
Oral, tab. Maximum dose, 100 mg. (1·5 gr.) daily for 2 weeks.
Intravenous in severe cases.

Dibistin (Ciba).
Sugar-coated tablets containing 0·05 *gm.* (0·7 *gr.*) *antistin and* 0·025 *gm.* (0·37 *gr.*) *pyribenzamine.*
A cream is also made for local application.
Has a double antihistamine effect in seasonal allergic conditions, solar dermatitis, pruritic dermatitis, hay fever, etc.

Dicophanum B.P. Add. *DDT.*
1 : 1 : 1-*trichloro*-2 : 2-*di-p-chlorophenylethane.*
Chronic poisoning arises from inhalation of dust or absorption through the skin. Causes loss of appetite, muscular weakness and fine tremors.
Insecticide and larvicide. Effective against head and body lice and typhus epidemics have been aborted by blowing mixture of 2–10% dicophane and talc between skin and clothing as dust, or as oily spray for mosquito control. Residual sprays of walls with 5% solution in paraffin oil. 10 c.c. per sq. yard effective for 4 months. For quick "knock down" pyrethrum is added to dicophane spray solutions.

Di-iodohydroxyquinoline B.P.

Diodoquin, Dihaloquin, Savorquin, Embequin.
Compound of quinoxyl with 63·9% iodine.

Chronic amœbiasis.
Oral, tab. 0·25–0·3 gm. (3·7–4·6 gr.) 3–10 daily for eradication of *E. histolytica cysts.*

Diphenan B.P. *Butolan, Oxylan.*

p-benzylphenyl carbamate.

Oxyuriasis.
Oral, 0·5 gm. (7·7 gr.) three times daily.

Diphétarsone. *Bémarsal.*

Intestinal amœbiasis and, when combined with chloroquine diphosphate, has given satisfactory results in malaria.
Oral, tab. Bemarsal, 2 gm. (30·8 gr.) with chloroquine 0·3 gm. (4·6 gr.) for 10 days.

Dithranol B.P. *Anthralin, Cignolin, Derobin.*

1 : 8-*dihydroxyanthranol.*

Oriental Sore, Ringworm skin affections.
As an ointment, 0·25–3%.

D.M.P. Dimethylphthalas, B.P.C.

Repellent for insects, mosquitoes, tick fleas and especially *Trombicula akamushi*, and other mite vectors of scrub typhus.

Clothing impregnated, but should not be used on artificial silks.
D.M.P. cream containing 35% D.I.M.P. repellent.

Emetine and Bismuth Iodide, B.P. E.B.I.

Bismuth iodide of emetine.

Amœbiasis.
Oral, 0·02–0·12 gm. (0·3–1·8 gr.). Total 1·5–2 gm. (23·1–30·8 gr.). In gelatin capsules (slipules); emplets, enteric-coated tablets, not recommended.

Emetine Hydrochloride B.P.

Emetine is alkaloid of ipecacuanha.

Amœbiasis, Liver Abscess, Oriental Sore, Clonarchiasis, Paragonimiasis.
Injection, deep subcutaneous or intramuscular.
0·06 gm. (1 gr.) usually in daily doses.
Total 6–12 gr. (0·38–0·77 gm.). Powerful effect in acute Amœbic Dysentery and in Amœbic Hepatitis.

Entacyl (B.D.H.).

Piperazine adipate.

Ascaris lumbricoides, Trichuris trichiura, Oxyuris vermicularis (thread worm).
Oral, tab. 300 mg. (4·6 gr.) 2 tab. three times daily. One tablet for each year of life. Children over six same dose as adults. For oxyuris continue for 7 days.
In syrup form for children.

Entamide. R.D. 3803.
Dichloracet-4-hydroxy-N.-methylanilide.
Amœbiasis.
Oral, tab. 12 mg. per kg. for 10 days.

Enterovioform (Ciba).
Iodochlorohydroxyquinoline with sapamine.
Infantile summer diarrhœa, colitis and Amœbic Dysentery.
Oral, capsules 0·75 to 1 gm. (11·5–15·4 gr.) in divided doses of 0·25 gm. for 10 days.

Erythromycin. *Ilotycin, Erythrocin, Erythromycin stearate.*
Antibiotic from Streptomyces erythreus.
Amœbiasis, Toxoplasmosis.
Oral, capsules. Dosage 300 mg. four times daily.

Etharsanol.
Sodium-4-β-hydroxyethylaminophenylarsonate.
Trypanosomiasis (*T. gambiense*).
Intravenous, 2 gm. (30 gr.).

Ethyl Esters of Hydnocarpus Oil B.P. *Antileprol, Chaulmestrol, Moogrol.*
A mixture of the ethyl esters of the unsaturated fatty acids (chiefly chaulmoogric and hydnocarpic acids) of hydnocarpus oil.
Leprosy.
Intradermal, subcutaneous or intramuscular, 2–5 c.c. (32·4 min. or 1·35 ʒ).

Folic acid. *Pteroylglutamic acid.*
Synthetic product resembling *Lactobacillus casei* factor of liver and yeast.
Produces hæmopoietic response in macrocytic anæmia.
Tropical sprue, Nutritional Tropical Macrocytic Anæmia.
Oral, tab. 5–30 mg. (0·07–0·46 gr.).
Folvite = Sodium salt for parenteral administration, 15 mg. per c.c. used in conjunction with liver extract for Pernicious Anæmia.

Fourneau, 710.
Plasmocide, Rhodoquine.
6. *methoxy-a-diethylamino-n-prophylaminoquinolene.*
Malaria.
Oral, tab. 0·02–0·04 gm. (0·3–0·6 gr.) for 7 days.

Fumagillin. *Fumidil.*
Antibiotic isolated from Aspergillus fumigatus.
Amœbic Dysentery. Active on cultures of *E. histolytica* 1 : 10 million.
Oral, capsules containing 10 mg. (0·15 gr.). Dose is 30–60 mg. (0·46–0·9 gr.) daily in divided doses, for 10 days.

Gammabenzene. *Benzene hydrochloride, Lindane, Gammexane, Lorexane.*
Application for nits active against mosquitoes, flies, lice and ticks.
Lotion contains: gamma benzene Hcl., gr. 1 (0·06 gm.); emulsifying wax, gr. 35 (2·26 gm.); xylene of commerce, min. 144 (8·9 gm.); lavender oil, min. 10 (0·6 gm.); water ad. fl. oz. 2 (60 c.c.).
Rub into hair and roots. Do not wash head for one day.
Benzene hexachloride ointment, ½%. Active and rapid cure for scabies.

Glaucarubin. (Merck, Sharp and Dohme.)
Derived from Simaruba glauca.
a-methyl-a hydroxy butyric acid combined with hexahydroxylactone.
Amœbiasis.
Oral, tab. 1 mg. per kg. for 10 days.

Guanimycin.
Mixture of Streptomycin and Sulphaguanidine. Streptomycin 5 *gm. Sulphaguanidine* 3 *gm.* (46·2 *gr.*) *per fluid ounce in suspending agent. Add* 1½ *fl. oz.* (45 *c.c.*) *of cold water and shake.*
Bacillary dysenteries.
Suspension. Oral. Two tablespoonfuls every four hours—children one tablespoonful every three hours.

Hetrazan (844). *Banocide, Notézine, Diethylcarbamazine B.P.C. Supp., Diaethylcarbamazine Citras Acidus.*
1-*diethylcarbamyl*-4-*methyl piperazine hydrochloride, and hetrazan and hydrogen-citrate* (*Banocide*).
Filariasis (*W. bancrofti, W. bancrofti* var. *pacifica, W. malayi*), *Loa loa, Onchocerca volvulus, Mansonella ozzardi, Dipetalonema perstans*, Larva migrans, *Ascaris lumbricoides*, Tropical Eosinophilia.
Oral, tab. 0·5–2 mg. per kg. three times daily. 100–300 mg. (1·5–4·6 gr.) for average adult.

Hexamine B.P.C. *Aminoform.*
Hexamethylene tetramine.
Urinary infections (*Bact. coli.*), Cholecystitis.
Oral, tab. 0·6–2 gm. (9·2–30·8 gr.).

Hexylresorcinol B.P.C. *Caprokol.*
1 : 3-*dihydroxy*-4-*hexylbenzene.*
Ascaris lumbricoides, Ancylostoma duodenale, Trichuris trichiura.
Oral, cachets or pills, 0·2 gm. (3 gr.) 5 daily.
Also 1 : 2,000 solution rectal enema for oxyuriasis.

Holarrhena B.P. *Kurchi, Coorchi.*
Contains the alkaloids conessine, holarrhenine, kurchicine and kurchine.
Amœbiasis.
Oral, 0·25–0·6 gm. (3·7–9·2 gr.). Preparation used in India.

Hydnocarpus Oil B.P.
Fatty oil obtained by cold expression from seeds of *Hydnocarpus wightiana.*
Leprosy.
Injection, intradermal, subcutaneous or intramuscular, 2–5 c.c. (32·4 min.–1·353).

Hydroxystilbamidine isethionate.
2-*hydroxy*-4 : 4′-*diamidinostilbene di*-(*B-hydroxyethanesulphonate*).
Kala-azar, particularly antimony resistant cases, Blastomycosis, *Candida albicans* infections, and other systemic fungal infections. Palliative for myelomatosis.
Intravenous, 3–5 mg. per kg. Adult dose 250 mg. in 10 c.c. water injected slowly daily, or on alternate days.

Injectio Bismuth B.P. *Bisglucol, Bismostab.*

20% W/V precipitated bismuth, 0·5% V/V cresol in isotonic dextrose solution.

Yaws, Syphilis.
Injection, intramuscular or deep subcutaneous, 0·5–1 c.c. (8·1–16·2 min.)

Injection of Bismuth Salicylate B.P.C. *Bisantol, Bismosan.*

10% suspension of bismuth salicylate in neutral vegetable oil.

Yaws, Syphilis.
Oral, tab. 0·6–2 gm. (9·2–30·8 gr.).
Injection, deep intramuscular or deep subcutaneous, 2 c.c. (32·4 min.) 60–200 mg. (1 c.c. = 0·051 Bi) 0·9–3 min.

Isoniazid. *Isonicotinic acid hydrazide, Nicetal, Nydrazid, I.N.H. (International Symbol).*

Derivative of *iso-nicotinic acid.*

Leprosy, Tuberculosis.
In combination with dapsone.
Oral, tab. 6–8 mg. per kg. Tab. and capsules 50 mg. (0·77 gr.).

Kaolin Leve B.P. *Light kaolin, Bolus alba, China clay.*

Cholera.
Oral, suspension 200 gm. (3086 gr.) in 400 c.c. (15·5 oz.) of water.
Mist. Kaolini et Morphinæ. Light kaolin 30 gr. (2 gm.), sodi bicarb. 10 gr. (0·64 gm.), tinct. chloroformi et morphinæ 10 min. (0·6 c.c.), water to ½ oz. (15 c.c.).

Kikuth's Sdt. 386B.

Arseno-stibio compound of the salvarsan type.

Bartonellosis.
Intravenous, 0·2 gm. (3 gr.).

Kousso. *Cusso.*

Dried female flowers of Brayera anthelmintica. Kusotoxin, active principle.

Tæniasis, *T. saginata*, in Abyssinia.
Oral, powder 1–4 gm. (15–60 gr.) in divided doses at half-hour intervals. Total dosage 8 gm. (123·4 gr.) followed by purgative. Effective if freshly prepared.

Lacquin. (Cow and Gate, Ltd.)

Milk powder containing quinine ethyl carbonate 2½ gr. (0·16 *gm.*) *to teaspoonful.*

Malaria.
Tasteless and suitable for children.

Magnamycin. *Carbomycin.*

Antibiotic derived from *Streptomyces halstedi.* Possesses amœbicidal action *in vitro.*

Amœbiasis, Toxoplasmosis.
Oral, capsules 1–2 gm. (15·4–30·8 gr.) daily for 6–10 days.
Dosis therapeutica 40–50 mg. per kg.

Male Fern B.P. *Filix Mas.*

Ether extract of dried rhizome and leaf bases of Dyopteris filix mas containing 25% W/W filicin.

Cestodiasis, *Tænia Saginata, T. solium* and *Diphyllobothrium latum.*
Oral, liquid 3–5·5 c.c. (48·6 mins.–1·4 ʒ) in syrup or in gelatin capsules, each containing 15 min., followed by saline aperient.

Mandelic Acid B.P.C.

a′-hydroxy phenylacetic acid, phenylglycollic acid.

Urinary infections, especially *Bact. coli.*
Oral, in syrup 2–4 gm. (30–60 gr.).

Melarsen oxide/BAL. *Melarsen B, Arsobal* (France and Portugal).

p-(2 : 4*-diamino-*1 : 3 : 5*-triazinyl-*6)*-aminophenyl arseno-γ : B-dithiopropanol.*
A trivalent arsenical compound.

Trypanosomiasis, especially for advanced cases due to *T. gambiense* and *T. rhodesiense.*
Intravenous, 1·8–3·6 mg. per kg. Adult dose 2·5—5 c.c. (40·5 mins.–1·35 ʒ) of 3·6% in propylene glycol daily for 3–4 days.
Second similar course one week later.

Melarsen sodium.

Monosodium salt of p-(2 : 4*-diamino-*1 : 3 : 5*-triazinyl-*6)*-aminophenylarsonic acid.*
A pentavalent arsenical compound.

Trypanosomiasis, due to *T. gambiense,* especially for late relapsing tryparsamide resistant cases.
Intravenous. Freshly prepared 10% solution.
Adults 1 gm. (15·4 gr.) adolescents 0·7 gm. (10·8 gr.). Children under 12 0·4 gm. (6·1 gr.) 8–12 injections at intervals of 5–7 days.

Mepacrine Hydrochloride B.P. *Atebrin, Quinacrine.*

2-chloro-5(w-diethylamino-a-methylbutylamino)-7-methoxyacridine dihydrochloride.

Malaria, especially *P. falciparum,* Oriental Sore, Giardiasis, Cestodiasis, *T. saginata, T. solium, D. latum,* Lupus erythematosus.
Oral, tab. 0·05–1 gm. (7·7–15·4 gr.) maximum loading dose 0·3 gm. (4·6 gr.) maximum daily dose for tapeworm 0·9 gm. (13·8 gr.).

Mepacrine Methane-Sulphonate B.P. *Atebrin musonate.*

Dimethanesulphonate of mepacrine.

Malaria, especially *P. falciparum,* Giardiasis.
Intramuscular or subcutaneous. Ampoules containing 0·12 and 0·36 gm.
Doses vary from 0·05 to 0·1 gm. (0·7–1·54 gr.).

Mesulphen B.P.C. *Mitigal, Sudermo (contains 25% of sulphur).*

2 : 6*-dimethylthianthrene.*

Scabies, Fungous infections of feet.
Local application of standard solution.

Milibis. *Wia, Wintadon, Bismuth glycolylarsinalate.*

Bismuth derivative of oxy-para-N-glycolyl-arsanilate. Contains 15·01% arsenic, 41·81% bismuth.

Chronic Amœbic Dysentery.
Oral, tab. 0·25 gm. (3·7 gr.) three times daily 7–16 days.

Miracil D. Leucanthone hydrochloride B.P.C. *Nilodin.*

Hydrochloride of 1-methyl-4-beta-diethyl-aminoethyl, aminothioxanthone.

Schistosomiasis, especially *S. hæmatobium.*
Oral, tab. 500 mg. (7·7 gr.) at twelve-hour intervals up to 14 days. Usual dose for adult is 1 gm. (15 5·4 gr.) (7mg. per kg.).
Blood concentration should be 300 mg. %.

Mycil (B.D.H.).

Mycil ointment, dusting powder, contains fungicide-chlorophenesin.

Mycil pessaries contain chlorophenesin and D.M. 238 (*hydroxy dichloro-diphenyl-methane*).

Fungicidal preparation.

Fungous infection of feet, *Tinea circinata, T. cruris, T. unguium.*

Mycostatin. *Nystatin.*

Antibiotic originally named fungicidin.

Coccidioidomycosis.
Has been shown to be fungistatic to cultures of *Coccidioides immitis.*

Myocrisin. *Sodium aurothiomalate.*

Relapsing Fevers, Lymphogranuloma inguinale, Clonorchiasis.
Injection, deep subcutaneous or intramuscular.
0·01–0·05 gm. (0·15–0·7 gr.) continued with 0·1 gm. (1·5 gr.) at weekly intervals.

Neoarsphenamine B.P.

Neosalvarsan, Novarsenobenzol.

Sodium 3 : 3′*-diamino-*4 : 4′*-dihydroxy arsenobenzene-N-methylene sulphoxylate.*

Relapsing Fevers (*S. recurrentis, S. duttoni*).
Rat-bite Fever (*S. minus*), Yaws, Syphilis, Malaria, Trypanosomiasis, Tropical Eosinophilia.
Intravenous, 0·15–0·9 gm. (2·3–13·8 gr.).

Neocryl. *Sodium succinanilo-methylamide-p-arsonate.*

Trypanosomiasis, Syphilis.
Intravenous 1·5 gm. (23·1 gr.) at stated intervals.

Neo-hepatex.

Proteolysed extract of liver for parenteral use. Contains also Vitamin B_{12} *in excess of 12 µmg. per c.c.*

Tropical Sprue, Nutritional tropical megalocytic anæmia, malarial anæmia.
Intramuscular, 2 c.c. (32·4 mins.) on alternate days.

Neomycin.
Antibiotic obtained from *Bacillus fradiæ.*
Consists of three antibiotics known as neomycin complex.
It is a good intestinal antiseptic and has been used successfully in the treatment of gram-negative urinary tract infections. Neomycin contains a nephrotoxic factor.

Neo-premaline.
An association of Chloroquine 0·15 *gm.* (2·2 *gr.*), *Pamaquin* 0·0075 *gm.* (1·07 *gr.*) *and Rhodoquine* 0·0075 *gm.* (1·07 *gr.*)*:* the latter French preparation allied to pamaquin also called, *Plasmocide* or Fourneau 710.
Malaria.
Oral, one tablet three times daily for 10 days.
Suppressive, two tablets once a week.

Neostam. *Stibamine glucoside.* (B.W. & Co.)
Nitrogen-glucoside of sodium p-aminophenyl-stibonate.
Kala-azar, oriental sore, Espundia.
Intravenous, 0·2 gm. (3·2 gr.) repeated at regulated intervals.

Neostibosan. *Von Heyden* 693.
Diethylamino-p-aminophenyl-stibinate.
Kala-azar, oriental sore, Espundia.
Intravenous, or intramuscular, 0·2 gm. (3 gr.) at frequent intervals up to total of 4 gm. (61·6 gr.).

Nicotamidum B.P. *Nicotinic acid amide.*
*Pyridine-*3*-carboxylic acid amide.*
Pellagra.
Oral, tablet 50–250 mg. (0·77–3·85 gr.) daily.

Nicotinic Acid B.P. *Niacin.*
*Pyridine-*3*-carboxylic acid.*
Pellagra, Ménière's syndrome.
Oral, tab. 50–250 mg. (0·77–3·85 gr.) daily. In serious cases also intravenous.

Nivaquine (M. & B.) is the trade name for Chloroquine sulphate. Nivaquine (chloroquine sulphate) is known as Nivaquine B in U.S.A. Nivaquine C is 3*-methyl-*4 *(diethylamino-pentyl) amino-*7*-chloroquinoline dihydrochloride* which also is active against all forms of malaria but is not procurable in Great Britain.

Nivembin (M. & B.).
Chloroquine-di-iodohydroxy-quinoline tablets, each containing chloroquine sulphate 65 *mg. and di-iodohydroxy-quinoline* 300 *mg.*
Amœbiasis and amœbic hepatitis.
Oral, tab. one three times daily.

Novobiocin. *Albamycin.*
Antibiotic isolated from *Streptomyces niveus* or *actinomyces.*
Identical with "*cathomycin*" and "*cardelmycin*" (*crystallinic acid*).
Effective against a number of gram-negative organisms and inhibits the growth of gram-positive cocci.

Oleoresin of aspidium.

Extract of Filix mas containing filicin.

Tapeworms:—*Tænia saginata* and *T. solium, Heterophyes heterophyes.*

Oral, ʒi (3·75 c.c.) in emulsion.

Paludrine.

Diquanil B.P. Proguanil, (4888).

N_1-*p-chlorophenyl*-N_5-*isopropylbiguanide acetate, lactate and monohydrochloride.*

Malaria in all forms for treatment and prophylaxis.

Oral, tab. 0·1–0·75 gm. (1·5–11·5 gr.) daily for 7–10 days.

Prophylaxis 0·1 gm. (1·5 gr.).

Pamaquin B.P.

Plasmaquine, Præquine.

6-*methoxy*-8(4-*diethylamino-i-methyl-butylamino*) *quinoline.*

Malaria—antirelapse treatment of benign tertian.

Efficient gametocide in subtertian.

Hæmolytic side-effects, especially in coloured races.

Oral, tab. 0·02–0·04 gm. (0·3–0·6 gr.) daily for 7 days.

Para-amino-benzoic acid. P.A.B.A.

Typhus and other prolonged infections.

Oral, tab. 12 gm. (185·1 gr.).

Pelletierine tannate.

Mixture of tannates of alkaloids obtained from pomegranate stem and root bark (Punica granatum) the chief of which are pelletierine and pseudo-pelletierine.

Tapeworms, *Tænia saginata, T. solium.*

Oral, tab. 0·12–0·5 gm. (1·8–7·7 gr.) followed after 2 hours by saline purge used as a substitute for *Filix mas.* Preceded for 2 days by three daily 30 gr. doses of sodium bicarbonate.

Penicillin B.P. A number of forms are known including G.F., K., X. and O.

Sodium or calcium salts from *Penicillum notatum.*

Procaine penicillin exerts more lasting effects.

(0·3–0·6 mega units daily) Penicillin aluminium monostearate (P.A.M.) recommended for yaws.

Bicillin effective for 2 weeks (N,N′-dibenzyl ethylene diamine dipenicillin G), also *Penicillin G* (Neopenil) (diethylaminoethyl ester hydriodide). Aqueous penicillin G and procaine penicillin are most frequently used.

Staphylococcal, streptococcal, gonococcal, pneumococcal and other gram-positive bacterial infections, also for treatment of Syphilis, Yaws, Ulcus Tropicum, Relapsing Fevers, Leptospiroses, Rat-bite Fever, and Nutritional megalocytic Anæmia.

Intramuscular injection of G is 500,000 units twice daily, and aqueous procaine penicillin 300,000 units once or twice daily.

Calcium salts can be given by mouth and used for topical application. Continued use of penicillin induces sensitivity in the patient and resistance in the organisms especially staphylococci.

Pentamidine Isethionas B.P.C. 800 (*M. & B.*), *Lomidine* (Fr.).

4 : 4-*diamidino-diphenoxy-pentane* (*B-hydroxethane sulphonate*).

A similar preparation is pentamidine dimethanesulphonate.

Trypanosomiasis, Kala-azar, Espundia.
Intramuscular 4 mg. per kg. dissolved in 3–4 c.c. water daily, or on alternate days. Course not less than 12.
Intravenous 2 mg. per kg. with limit of 100 mg. per injection.
Given slowly with caution owing to fall in blood pressure.
In ampoules of 200 mg. (3 gr.); containers of powder each of 2 gm. (30·8 gr.).

Pentaquine. S.N. 13,276. *Isopentaquine, Primaquine.*
(6 *methoxy*-8(5-*isopropylamino amylamino*) *quinoline.*)
Malaria, especially relapsing benign tertian.
Oral, antirelapse treatment, tab. 60 mg. (0·9 gr.) with 20 gr. (1·29 gr.) quinine sulphate daily for 14 days.

Phenothiazine B.P.C. *Phenovis, Thiodiphenylamine.*
Dracontiasis (Guinea-worm).
Deep subcutaneous, injected in oily solution in 1 gm. doses in vicinity of guinea-worm. Formerly used for oxyuriasis in children, but is too toxic. Tab. by mouth, 0·5 gm. for *œsophagostomum.*

Phthalylsulphathiazolum B.P.C. *Thalistatin, Thalazole.*
2[*p*-(o-*carboxybenzol*)-*aminobenzene sulphamide*] *thiazole.*
Bacillary dysenteries, Ulcerative Colitis, Infantile gastro-enteritis, Chronic amœbic dysentery, pre- and post-operative use in intestinal surgery.
Oral, average dose 0·5–2 gm. (7·7–30·8 gr.). In acute bacillary dysentery 3–4 gm. daily—higher doses given in surgery.

Piperazina. *Piperazine hydrate, Antepar Elixir* (B.W. and Co.).
Oxyuriasis, Ascariasis, especially in children.
In syrup 50–75 mg. (0·7–1·37 gr.) per kg. per day. ⅛ gr. (0·008 gm.) daily per year of life.
(*See also* Entacyl.)

Plaquenil.
7-chloro-4 [4(*N-ethyl-N-B-hydroxyethylamino*) *quinoline diphosphate*].
Malaria.
A member of the 4-aminoquinoline group and probably as effective as chloroquine.

Polymyxin.
A general term for an antibiotic mixture, produced from Bacillus polymyxia. It has been shown to have at least four antibiotics—poliomyxin, a, b, c, d.
Polymyxin *b* is of most value. It is highly active against gram-negative bacteria.

Premaline " N."
An association of Mepacrine 0·1 *gm.* (1·5 *gr.*), *Rhodoquine* 0·005 gm. (0·07 *gr.*) *and Pamaquin* 0·005 *gm.* (0·07 *gr.*).
Malaria.
Oral, tab. One tablet three times daily for 7 days.
Suppressive, three tablets once a week.

Primaquine. S.N. 13,272.
8 aminoquinoline, allied to pamaquin.
Malaria, especially resistant relapsing cases of benign tertian.
Oral, tab. 0·015 gm. (0·22 gr.) daily for 14 days combined with quinine as suppressant. In larger doses toxic, especially to coloured people.

Promanide. *Prominin U.S.A.*
Sodium 4 : 4′-diaminodiphenyl sulphone. N-N′-didextrose sulphonate.
Leprosy, Tuberculosis
Intravenous 1–5 gm. (15·4–77·1 gr.) daily: increase gradually. Can be continued for long periods. May produce severe hæmolytic anæmia.

Promizole.
4 : 2′-diamino diphenyl-5′-thiazolylsulphone.
Leprosy, Tuberculosis.
Oral, tab. 0·5–0·6 gm. (7·7–9·2 gr.) daily increasing gradually up to 6 gm. (92·5 gr.). Low toxicity.

Propanarsol
Monosodium salt of 3-p-arsono-anilino-propono
Trypanosomiasis (*T. gambiense*).
Intravenous, 2 gm. (30·8 gr.).

Puromycin, antibiotic obtained from *Streptomyces alboniger* has been used for Chagas' disease (*T. cruzi*) in Chile.

Quinidine Sulphate B.P *Quinicardine.*
Cinchona alkaloid isomeric with quinine.
Malaria. Auricular fibrillation.
Oral, tab. 0·2–0·6 gm. (3–9·2 gr.). In same doses as quinine for benign tertian malaria.

Quinine Bisulphate B.P.
Malaria.
Oral, tab. 0·06–0·6 gm. (0·9–9·2 gr.) two or three times daily.
Easily soluble in water.

Quinine Dihydrochloride B.P. Quinine *bihydrochloride.*
Malaria.
Oral, intravenous or intramuscular 0·3–0·6 gm. (4·6–9·2 gr.) two or three times daily.

Quinine Hydrochloride B.P.
Malaria.
Oral, tab. 0·06–0·6 gm. (0·9–9·2 gr.) two or three times daily; also injected intravenously.

Quinine Sulphate B.P.
Malaria, Night cramps.
Oral, tab. 0·06–0·6 gm. (0·9–9·2 gr.). To dissolve in water add dilute H_2SO_4.

Quinine and Urethane Injection B.P *Varixol.*
Sterile aqueous solution containing quinine Hcl. 13·33%, *urethane* 6·67%.
Subtertian malaria, Varicose Veins.
Intravenous or intramuscular, 5 c.c. (1·35 3).

Quiniplex.

A mixture of pentaquine and quinine sulphate.

Benign tertian malaria.

Oral, tab. containing 150 mg. (2·3 gr.) quinine sulphate, plus 6·5 mg. (9·9 gr.) pentaquine phosphate, 6 daily for 14 days or longer to prevent relapses.

Resotren.

Neutral salt of one molecule of resochin (chloroquine) and two molecules of quinoxyl (yatren) acid forming a stable compound of low solubility.

7-chlor-4-(4′diethylamino-1′-methyl-butylamino)-quinoline-di-7-iodo-8-oxquinoline-5-sulphonate.

This salt is hydrolysed in intestine, liberating quinoxyl and absorbable resochin.

Amœbic Dysentery, Amœbic Hepatitis and Hepatic Abscess.

Oral, tab. 0·5 gm. (7·7 gr.) 1 tab. 4 times daily, subsequently 3 times for 7 days.

Riboflavina B.P. *Vitamin* B_2, *Lactoflavin.*

6 : 7 Dimethyl-9-(d-l′-ribityl)-iso-alloxazine.

Ariboflavinosis, Pellagra.

Oral, tab. 5–10 mg. (0·07–0·15 gr.) daily. Larger doses in acute conditions.

Rivanol.

2-ethoxy-6 : 9-diaminoacridine lactate.

Chronic bacillary dysentery.

Oral, tab. 0·1 gm. (1·5 gr.). Rectal retention enemata 0·1%, usually given in 1 : 500–1 : 2,000 solution.

Rovamycin. *Spiramycin.*

French antibiotic derived from *Streptomyces ambofaciens.*

Probably has wide range of activity in tropical diseases, mostly in Typhoid and Plague, streptococcal, staphylococcal and pneumococcal infections.

Oral, capsules. Adults 2–5 gm. (30·8–77·1 gr.). Children 50–100 mg. per kg. subdivided into doses at 6–8 hour intervals.

Santoninum B.P

$C_{15}H_{18}O_3$ *Santonica.*

Dried unexpanded capitula of Artemesia maritima var. anthelminticum.

Ascaris lumbricoides.

Oral, tab. 0·06–0·3 gm. (0·9–4·6 gr.) usually prescribed in combination with calomel.

Toxic effects on vision. White objects looking at first violet, later yellow (xanthopsia).

Simaruba. *Dried root-bark of S. amara.*

Infusion of 15 gr. (1 gm.) to ounce of boiling water for 15 minutes.

Chronic amœbic and bacillary dysenteries.

Oral, tab. 1–2 gm. (15·4–30·8 gr.).

Sobita. (Howards.)

Sodium bismuth tartrate.

Yaws.

Injection, intramuscular, 1–2 gm. (15·4–30·8 gr.) in 10% solution 2 c.c. (32·4 min.).

Solganal B oleosum. *Aurothioglucose*

Relapsing Fevers, Lymphogranuloma inguinale, clonorchiasis.

Injection intravenous or intramuscular, 0·1–0·4 gm. (1·5–6·1 gr.).

Soluseptasine B.P.C.

Disodium-p-(γ-phenylpropylamino)-benzenesulphonamide-α-γ-disulphonate.

Filarial lymphangitis (*W. bancrofti*).

Injection, intravenous 1 gm. (15·4 gr.) in 10 or 20% solution.

Solustibosan *Sodium antimony gluconate, Pentostam, Sodium stibogluconas B.P.C.*

A pentavalent antimony compound of hexonic acid.

Kala-azar, Oriental Sore, Espundia.

Intravenous, or intramuscular. 6 c.c. contains 2% antimony (0·126 gm.–1·8 gr.). A course of 10 daily injections well tolerated.

Solvochin.

A 25% water soluble basic quinine preparation for intramuscular injection with pH adapted to reaction of tissues: dissolved in phenazone.

Malaria, especially pernicious forms of subtertian.

Intramuscular, 2·2 c.c. (35·8 min.) twice daily for 4 days maximum. Each ampoule contains 0·5 gm. (7·7 gr.) quinine. Causes little local reaction.

Sontochin. *S.N.* 6911, 3038 *R.P., Sontoquine, Santoquine.*

(7-*chloro*-4 (4-*diethylamino*-1 *methylbutylamino*)-3-*methylquinoline*) *disulphate and monohydrate salts.*

Malaria.

Much used in Germany. Dosage and action similar to that of chloroquine.

Stibamine.

Sodium p-aminophenylstibinate.

Kala-azar.

Intravenous, 0·1–0·2 gm. (1·5–3 gr.) total dosage, 6–10 gm. dissolved in 10 c.c. (2·7 ʒ) distilled water on alternate days.

Stibophenum B.P.

Fouadin, Neoantimosan.

Sodium-antimony-bispyrocatechol-3 : 5-*sodium disulphonate.*

Contains 13·5% *antimony in trivalent form.*

Schistosomiasis, Lymphogranulome inguinale, Leishmaniasis, Filariasis.

Intravenous and intramuscular, 0·1–0·3 gm. (1·5–4·6 gr.) in 7% solution 1·5 c.c., 3·5 c.c., 5 c.c. (1·3 ʒ) on consecutive days, then 5 c.c. (1·3 ʒ) on alternate days. Total 40 c.c. (1 oz. 2 ʒ)

Stibosan. *Von Heyden* 471.

Sodium-m-chlor-p-acetylaminophenylstibinate.

Kala-azar, Rat-bite Fever.
Intravenous or intramuscular, 0·2 gm. (3 gr.).
Total dosage 6–10 gm. (92·5–154 gr.) on alternate days.

Stilbamidinæ isethionas. M. & B. 774, *Diamidino-stilbene.*

Used in form of B-hydroxyethanesulphonate.

Kala-azar.
Intravenous in *Indian* form:—0·04 (0·6 gr.), 0·075 (1·05 gr.), 0·09 (1·35 gr.), 0·12 (1·8 gr.), 0·14 (2·1 gr.), 0·15 gm. (2·2 gr.) in single course of 10–15 injections. For children initial dose of 0·015 gm. (0·22 gr.).
Sudan form: 1·5–3·5 mg. per kg. 15 daily injections separated by 7-day intervals. Total dosage: 3–4·8 gm. (46·2 –74 gr.). Late neuropathies have frequently been reported after treatment.

Stovarsol. *Acetarsol B.P., Spirocid, Acetarsone.*

3-*acetylamino*-4-*hydroxyphenylarsonic acid.*

Relapsing Fevers, Rat-bite Fever, Trypanosomiasis, Yaws, Syphilis, Tropical Eosinophilia, Giardiasis, Balantidiasis, Trichomonas.
Oral, tab. 0·06–0·25 gm. (0·92–3·7 gr.) two or three times daily for 10–12 days. Prolonged treatment may give rise to arsenical poisoning.

Streptomycini Sulphas B.P. Add.

Antibiotic isolated from *Actinomyces griseus*, employed as the sulphate.
Meso-1-3-*diguanidino*-2, 3, 4, 6, *tetrahydroxy-cyclorexane glucoside of a disaccharide.*

Active entirely against gram-negative organisms.
Tuberculosis, Plague, Tularæmia, Ulcerating Granuloma of Pudenda, "Q Fever," Bacillary Dysenteries, *Bact. coli* infections, Meningitis, Whooping Cough, Actinomycosis and Gonorrhœa.
Intramuscular in solution 0·5 gm. of the base daily.
Oral in cachets, 250 mg. (3·7 gr.) four times daily for intestinal infections taken with a cup of milk or water.
The following preparations are in use: *Streptomycini et Calc, chloridum, Injectio Streptomycini et Calc. chloridi, Streptomycini Hydrochloridum, Streptomycini sulphas* and *Injectio Streptomycini sulphatis.*

Dihydro Streptomycinum (*B.P. Add*).

Consists of the hydrochloride or the sulphate.

May be given to patients who have become sensitized to streptomycin.
Causes more vestibular damage than parent substance. Streptomycin is toxic to the vestibular branch of the 8th cranial nerve.

Succinyl-Sulphathiazolum B.P. *Sulphasuxidine, Colistatin.*

2(*p-succinyl-amino benzenesulphonamido*) *thiazole.*

Bacillary Dysenteries, Ulcerative Colitis.
Oral, tab. or powder, 10–14 gm. (154–216 gr.). Initial dose 4 gm., followed by maintenance dose of 2 gm. (30·8 gr.) 4 times daily. American workers advocate larger doses up to 0·25 gm. (3·7 gr.) per kg. for pre- and post-operative treatment.

Sulphadiazina B.P.

2.(*p-aminobenzenesulphonamido*)-*pyrimidine.*

Pneumonia, Plague, Filariasis, Bacillary Dysenteries, Lymphogranuloma inguinale, Melioidosis.

Oral, tab. 1–4 gm. (15·4–61·7 gr.). Initial dose 4 gm. (61·7 gr.) followed by 1 gm. every four hours. Has low toxicity.

Sulphadimidine B.P. *Sulphadimethylpyrimidine, Sulphamezathine.*

2-(4-*aminobenzenesulphonyl-amino*-4 : 6-*dimethylpyrimidine*).

Pneumonia, Bacillary Dysenteries, Ulcerative Colitis.

Oral, tab. 2 gm. (30·8 gr.). Initial dose = 1 gm. (15·4 gr.). Subsequently every 6 hours for 5–7 days.

Sulphaguanidina B.P. *Sulphanylguanidine.*

p-aminobenzenesulphonylguanidine-monohydrate.

Bacillary Dysenteries especially *S. shigæ.* infections.

Oral, tab. 0·3 and 0·5 gm. Individual dose 2–4 gm. (30·8–61·7 gr.). Initial dose = 0·1 gm. per kg. Maintenance dose = 0·05 gm. per kg. Total dosage in severe case = 130 gm. (2006 gr.).

Sulphamerazina B.P.C. *Sulphamethydiazine.*

Resembles sulphadiazine in general properties.

Bact. coli infections of the urinary tract for which its solubility makes it specially suitable.

Oral, tab. 0·5 gm. (7·7 gr.). For acute infections in adults, 3–4 gm. (46·2–61·7 gr.) followed by 1·0 gm. (15·4 gr.) every 8 hours continued every 8 hours till clinical response is obtained.

For children 3–10 years, 1·5 gm. (23·1 gr.) followed by 1 gm. (15·4 gr.) Under six months 0·5 gm. (7·7 gr.) followed by 0·25 gm. (3·8 gr.) every 12 hours.

Sulphapyridina B.P.C. (*M. & B.* 693), *Sulphiadine.*

2-(*p-aminobenzenesulphamido*)-*pyridine.*

Pneumonia, Gonorrhœa, Cerebrospinal meningitis, Lymphogranuloma inguinale, Bubonic plague, Streptococcal infections, Dermatitis herpetiformis.

Oral, tab. 0·5–2 gm. (2·7–30·8 gr.) followed by 1 gm. (15·4 gr.) 4 hourly for 2 days, then 1 gm. (15·4 gr.) 6 hourly for 2 days.

Sulpharsphenamina B.P. *Myosalvarsan, Sulpharsenol, Sulpharsenobenzene, Sulphostab.*

Disodium-3 : 3′-*diamino*-4 : 4′-*dihydroxyarsenobenzene-N* : *N′-dimethylsulphate.*

Relapsing fever, Yaws, Syphilis, Trypanosomiasis.

Injection, intramuscular or intravenous, 0·1–0·6 gm. (1·5–9·2 gr.).

Sulphathiazolum B.P. *Thiazamide, Cibazol.*

2-(*p-aminobenzenesulphonamido*)-*thiazole.*

Pneumonia, Malaria, Plague, Filariasis, Lymphogranuloma inguinale.

Oral, tab. 2 gm. (30·8 gr.) initially; 1 gm. (15·4 gr.) every 4 hours.

Sulphatriad. (*M. & B.*)

An association of sulphathiazole 0·37 *gm.* (5·6 *gr.*), *sulphadiazine* 0·37 *gm.* (5·6 *gr.*) *and sulphamerazine* 0·26 *gm.* (3·9 *gr.*) *per gm. for systemic sulphonamide therapy with reduced risk of crystalluria.*

Oral, tab. 2–4 gm. (30·8–61·7 gr.). Course as for other active sulphon amides.

Sulphetrone. *Solapsonum B.P.C.*

Tetrasodium-4-4′-di-phenylpropyl-amino-diphenyl sulphone tetra-sulphone.

Leprosy, Tuberculosis.

Oral, tab. initial dose 1·5 gm. (23·1 gr.) gradually increasing to 6–9 gm. (92·5–138·8 gr.) daily.

Toxic effects nausea, vomiting, depression, drug rash and hypochromic anæmia frequently.

Teropterin.

Pterolyl-y-glutamyl-y-glutamyl glutamic acid.

Sprue, Pernicious Anæmia, Carcinoma.

Intramuscular injection, 10–20 mg. (0·15–0·3 gr.) daily.

Ampoules of 1 c.c. containing 10 mg. (0·15 gr.) injected daily for one week.

Terramycinum. *Oxytetracycline.*

Antibiotic isolated from cultures of Streptomyces rimosus.

Amœbiasis (chronic), Typhus Fevers, Salmonella Infections, *Bact. coli* infections, Oxyuriasis, Balantidiasis, Tropical Ulcer, Yaws, Anthrax, Undulant Fevers.

Oral, capsules of 250 mg. (3·7 gr.) 2 gm. daily (30·8 gr.) in divided doses. Treatment continued for 48 hours after temperature has become normal.

Intravenous 0·5–1 gm. daily in divided doses.

Tetrachlorethylenum B.P. *Perchlorethylene Ethylene tetrachloride.*

Ancylostomiasis, Oxyuriasis, *Hymenolepis nana.*

Oral, capsules containing 1 c.c. (16·2 min.).

Dose 1–3 capsules. In liquid form 3 c.c. (48·6 min.) prescribed with oil of chenopodium.

Tetracycline. *Achromycin, Tetracyn, Polycycline.*

A broad-spectrum antibiotic prepared by reduction from Aureomycin (*chlortetracycline*) (*q.v.*). Antibacterial activity similar to that of chlortetracycline and oxytetracycline but causes fewer side-effects and is more stable.

Effective against numerous Gram-positive and Gram-negative organisms, Undulant fevers, Typhus, Q fever, Lymphogranuloma venereum, Psittacosis, Amœbiasis, Yaws, Coccidioidomycosis.

Oral, 250–500 mg. 4 times daily.

Injection, intramuscular, 200–300 mg. daily in divided doses at 8–12 hour intervals; intravenous, 500 mg. 12 hourly by drip as 0·1% solution.

Tetraethyliurammonosulphide. *Tetmosal.*

Scabies.

When combined with soap in 5–20% dilution, it retains its sarcopticidal properties.

Thiacetazonum. *Thiosemicarbazone.*

p-acetylaminobenzaldehyde thiosemicarbazone.

Tuberculosis, Leprosy.
Oral, tab. 0·1–0·2 gm. (1·5–3 gr.) daily.
Injection dissolved in 1–2 c.c. (16·2–32·4 min.) glycerin.
Tolerated dose = 2 mg. per kg.
Initial dose in leprosy sometimes as high as 50 mg. (0·7 gr.) increased over 4–8 weeks to 150 mg. (2·2 gr.).
Liable to produce toxic effects, rashes and anæmia.

Thio-bismol. *Bismuth Sodium Thioglycollate.*

Benign Tertian Malaria.
Injection, intramuscular 0·2 gm. (3 gr.).

Thiomersal. *Thiomersalate B.P.C., Merthiolate, Sodium ethylmercurithiosalicylate.*

Ringworm, *Tinea circinata*, etc.
In form of ointment or in alcoholic solution 0·1%.

Thymol B.P.

3-methyl-6-isopropylphenol.

Ancylostomiasis.
Oral, tab. 3–4 gm. (46·2–61·7 gr.).

Totaquina B.P.

Mixture of cinchona alkaloids containing not less than 70% alkaloids of which not less than one-fifth is quinine.
Type I. Quinine, cinchonine, cinchonidine.
Type II. Quinine, quinidine, cinchonine, cinchonidine.

Malaria.
Oral, tab. 0·06–0·6 gm. (0·9–9·2 gr.) two to three times daily.

Trichlorethylenum B.P.

Trilene.

Ancylostomiasis, Oxyuriasis.
Oral, liquid 2–3 c.c. (32·4–48·6 min.) in capsules or mixture. Contra-indicated in heart or kidney disease.

Triostam. *Trivalent sodium antimonylgluconate.*

Schistosomiasis *S. hæmatobium*, *S. mansoni* and *S. japonicum.*
Intravenous, 180 mg. (2·7 gr.) injected every day for 6 days. 6% solution 15–20 mg. (0·22–0·3 gr.) per kg. For man of 60 kg. dosage 200 mg. (3 gr.). Oral, can be given in 100 mg. doses in enteric coated tablets.
Solution must not be heated.

Tryparsamidum B.P. *Tryparsone.*

Sodium N-phenylglycineamide-p-arsonate.

Trypanosomiasis, *Trypanosoma gambiense*, *T. rhodesiense*, Neurosyphilis.
Intravenous or intramuscular injections.
1–2 gm. (15·4–30·8 gr.) on alternate days or at definite intervals.
Maximum 60 mg. per kg.
Total dosage 24 gm. (369·8 gr.).

Urea stibamine. *Stiburea.*

Combination of urea and p-aminophenylstibinic acid.

Kala-azar, other forms of leishmaniasis, Filariasis, Schistosomiasis.
Safer than tartar emetic.
Intravenous or intramuscular, ampoules of 50 (0·7 gr.), 100 (1·5 gr.), and 200 mg. (3 gr.). Dose 100–200 mg. (1·5–3 gr.) on alternate days.

Vitamin B_{12}. *Cyanocobalaminum B.P.C. Cytamen.*

Pernicious Anæmia, Nutritional Macrocytic anæmia, Tropical Sprue, Macrocytic Anæmia of pregnancy.
Intramuscular injection of 100 μmg.

Win. 5647, *Mantomide.*

N-(2-4 Dichlorobenzyl)-N-(2-Hydroxyethyl) Dichloracetamide.

Powerful amœbicide (*E. histolytica*).
Oral—under 5 years, 250 mg. (3·7 gr.) t.d. for 8 days; 5–10 years, 500 mg. (7·7 gr.) t.d. for 10 days; over 10 years, 750 mg. (11·5 gr.) t.d. for 10 days.

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